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CHRONIC PULMONARY OSTEOARTHROPATHY

DYSPITUITARISM AS A PROBABLE CAUSE

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NEW YORK

Since Hippocrates reported his observation on the occurrence of fusiform swelling of the terminal phalanges in persons with consumption this phenomenon has been noted repeatedly by physicians, who, though ignorant of its pathogenesis, nevertheless attached great significance to its appearance in wasting patients. The French physician Pigeaux [1] wrote in 1832: "The secret and almost mysterious relationship between phthisis and the state of nails evidently shows that older physicians were inclined to attach importance to small details which even in the 19th century represent elements of good diagnosis."

Interested in small details, physicians of the past overlooked, however, another detail, namely, that fusiform thickening of the phalanges sometimes accompanies a diffuse involvement of the skeleton. When similar widespread lesions were observed, they were not associated with the clubbed fingers and were not looked on as a sequel of a visceral disease, such as a disease of the lungs or heart, but were considered as a malady *sui generis*. Indeed, to the latter part of the nineteenth century chronic pulmonary osteoarthropathy was confused with arthritis deformans, acromegaly, Paget's disease of the bones and leonthiasis ossea and even with osteomalacia, which was not rare in those years.

Bamberger, in a brief presentation before the *Wiener medizinischer Gesellschaft* in 1889, was the first to record the observation that his patients with clubbed fingers also displayed a thickening of the hands, wrists, feet and legs. Moreover, he found the condition not only in tuberculosis, a belief hitherto entertained, but in bronchiectasis, empyema and congenital heart diseases. Almost simultaneously there appeared an article by Pierre Marie,[2] whose aim was chiefly to clear away misconceptions. "I wish at first," wrote the French clinician, "to clear the field of acromegaly of facts not germane to it." He first reviewed a case of a condition reported by him previously as acromegaly and found it to be a separate entity. By analyzing this case and those with identical symptoms available in the literature he stressed that in all of them the skeletal deformity and the clinical features were not characteristic of acromegaly; also that they were invariably preceded and accompanied by a long-standing disease of the lungs. He then expressed the opinion that the peculiar overgrowth of the bones in these cases, which he labeled *osteo-arthropathie hypertrophiante pneumique,* resulted from a primary pulmonary disease. Bamberger,[3] in another and more detailed paper, published in 1891, corroborated Marie's findings.

From the Division of Pulmonary Diseases, Montefiore Hospital.

Aided by a grant from the Rose Lampert Graff Foundation, Los Angeles.

1. Pigeaux, J.: Arch. gén. de méd. **29**:174, 1832.
2. Marie, P.: Rev. de méd. **10**:1, 1890.
3. Bamberger, E.: Ztschr. f. klin. Med. **18**:193, 1891.

As Paget's disease of the bones was isolated even before Marie's classic description of acromegaly, it ensued that a group of diseases formerly classed with it clinically was dissociated. Moreover, while the pathogenesis of Paget's disease remained obscure, as it still is today, that of acromegaly and of chronic pulmonary osteoarthropathy was thought to have been elucidated. Acromegaly was ascertained to result from an adenoma of the anterior part of the hypophysis, and osteoarthropathy was attributed to circulatory disturbances in the pulmonary circuit or to toxins emanating from the long-standing infection of the lungs.

While the etiologic relationship between the pituitary gland and acromegaly is no longer contested, the causative factor of chronic pulmonary osteoarthropathy remains problematic.

The 4 cases which I had the opportunity of studying in recent years have revealed features which would suggest that contrary to general belief the cause of chronic pulmonary osteoarthropathy may not be remote from that of acromegaly and that here too one is probably dealing with an endocrinopathy caused by a disease that originated primarily in the lungs.

REPORT OF CASES

CASE 1.—*History.*—A carpenter aged 45 years entered the Montefiore Hospital for the first time on Oct. 8, 1932, complaining of pain in the left side of the chest, swelling of the hands and feet and weakness. He neither smoked nor indulged in alcohol. He was married, and his wife and child, 5 years old, were in good health, as were his mother and twelve brothers and sisters. His father died at the age of 73 of carcinoma of the stomach.

The patient became ill in January 1932, experiencing a general malaise accompanied by fever and cough, productive of a small amount of sputum. As treatment at home led to no improvement, he was hospitalized in the middle of April 1932. At this time there were migratory pains in the joints of his hands and feet and pain in the precordium radiating to the shoulder. It was noticed that his left eye was ptotic and that his fingers and toes were noticeably clubbed.

The roentgenograms revealed a dense shadow at the apex of the left lung, which was interpreted as an old tuberculous lesion. The right knee joint showed considerable periarticular thickening and hypertrophy of the synovial membrane with some thickening of the suprapatellar bursa. The left showed in addition an inferior suprapatellar bursitis. The lower under surface and the shafts of the humeri, the radiuses and the ulnas showed productive periostitis. The laboratory data were noncontributory. He was discharged from the hospital with the diagnosis of fibroid phthisis and chronic pulmonary osteoarthropathy.

His health grew worse, and in July 1932 he was hospitalized in another institution, where his hands and feet were found to be "tremendously swollen." A considerable degree of clubbing and cyanosis of the fingers and toes were also recorded. There was swelling but not pitting edema of the soft tissues of the hands and feet extending above the wrists and ankles. A roentgenogram of the lungs showed a complete "veiling" of the left apex; the long bones of the hands and feet showed "marked periosteal infiltration." In this hospital, too, the diagnosis was tuberculosis of the apex of the left lung and osteoarthropathy.

The man's health declined, and he lost weight (12 Kg. in one year). On one occasion he had a small hemoptysis. On Oct. 8, 1932 he was admitted to the Montefiore Hospital.

Examination.—The patient was a tall, well developed man showing evidence of recent loss of weight; he weighed 58 Kg. No dyspnea or orthopnea was noted. His skin was dry but normally warm. His lower jaw was prognathic (fig. 1) and his hands and feet massive; the fingers showed clubbing. The chest was asymmetric, the left hemithorax being flatter than the right. The left supraclavicular and infraclavicular fossae were prominent and tender on palpation. The peripheral blood vessels were not enlarged, and there was no superficial edema. The left lung showed decreased vocal fremitus over the apex, extending down to the second rib anteriorly and to the third rib posteriorly. The percussion note was nearly flat; the voice and breath sounds were diminished, but there were no rales. The skin of the forehead showed considerable furrowing. The abdominal and pelvic viscera and the genitalia showed no abnormalities. There was pain in the left shoulder joint and arm, and motion was limited. The left eye showed Horner's syndrome (fig. 1). The results of the neurologic examination were normal. The diagnosis was carcinoma of the upper lobe of the left lung and chronic pulmonary osteoarthropathy.

A roentgenogram of the chest taken October 11 showed a dense shadow in the apical region extending from the apex down to and just beyond the first rib anteriorly. The shadow was sharply delineated (fig. 1). The diagnosis was: primary neoplasm of the lung. Roentgen examination of the left shoulder showed periosteal thickening along the shaft of the clavicle, arthritic changes involving the bone forming the shoulder joint and thickening of the periosteum

Fig. 1 (case 1).—Tumor of the left superior pulmonary sulcus (bronchiogenic cancer). Roentgenogram of the right hand and the left foot, showing extensive wartlike periosteal overgrowth and tufting of the terminal phalanges. In the inset is the patient's "oval" face, showing prognathism and left Horner's syndrome.

along the shaft of the humerus. A pronounced osteoarthropathy was present in the hands, all the bones appearing considerably broadened and somewhat shorter than normal, with a high degree of periosteal reaction and some sclerosis of bone. The feet, too, showed the same pathologic process (fig. 1). There was tufting of the terminal phalanges of the hands and feet. The basal metabolic rate was + 15 per cent.

The patient ran a downward course. The Horner syndrome became more accentuated. There occurred a destruction of the first, second and third ribs on the left side and erosion of the left border of the corresponding vertebrae. Paraplegia developed, and the patient died.

Necropsy.—Gross Examination: The body measured 168 cm. The lower jaw was prognathic. The hands and feet were voluminous and showed extreme clubbing of fingers and toes, with very slight edema. The edge of the liver extended 4 cm. below the right costal margin in the mamillary line. The right lung was free of adhesions, but the left was densely adherent to the chest wall above the hilum. The apical segment of the left lung was replaced by firm tissue which on separation from the anterior portion of the wall of the chest was found to extend up to the base of the neck on the right side, compressing the trachea. There was invasion by tumor of the sternal portion of the first rib and of the posterior portions of the first three ribs. The left side of each of the first three dorsal vertebrae was also eroded.

The heart weighed 470 Gm. The pericardial sac was adherent to the upper portion of the left lung. The myocardium was brownish red and firm. Both ventricles were dilated and hypertrophied, but the valves and the coronary arteries were normal. The pulmonary ring measured 8 cm.; the mitral, 10 cm., and the tricuspid, 14 cm. The thickness of the wall of the left ventricle varied from 8 to 13 mm. and that of the right from 2 to 4 mm. The pulmonary vessels were widely patent. The aorta showed occasional small atheromatous plaques.

The right lung was normal and the pleural cavity patent. In the left lung, beginning 2 cm. below the level of the bifurcation of the main bronchus, the upper lobe was replaced by a fairly well circumscribed tumor. The secondary branches of the upper lobe bronchus were largely obliterated by the neoplasm. The tracheobronchial lymph nodes were firm but contained no tumor. The blood vessels in both lungs were normal. No metastases were present in other parts of this lung or in the right lung, and no abnormalities were noticed in the bronchi throughout the lungs.

The liver weighed 2,000 Gm. and measured 20 by 9 by 8 cm. The right adrenal gland weighed 17 Gm., and the left weighed 10 Gm. A minute tumor nodule was visible in each adrenal. The right kidney weighed 280 Gm. and measured 14 by 7 by 5 cm. The left kidney weighed 340 Gm. and measured 14 by 8 by 6 cm. Both kidneys appeared large and firm but showed no invasion by tumor tissue. The thyroid, too, was considerably enlarged, but there were no visibile abnormalities. The testes were small and firm.

The brain and the meninges revealed no gross pathologic changes. The sella turcica was conspicuously enlarged, and the pituitary was twice its normal size.

Microscopic Examination: Histologic sections showed a stratified squamous epithelial carcinoma of moderate malignancy. Tumor cells were present in the perivascular lymphatics and occasionally in the outer coat of the wall of some vessels. The adrenals contained a few minute clumps of metastatic tumor cells. The striated muscle of the heart showed hypertrophy and fragmentation. The liver showed increase in fibrous tissue in the periportal areas but no proliferation of the bile ducts; the configuration of the lobule was preserved. The spleen showed areas of amyloid. There was atrophy of the testes, with no spermatogenesis. In the pituitary there were hypertrophy and extensive proliferation of the eosinophilic cells.

Comment.—The principal lesion in this case was a carcinoma of the left pulmonary apex, a so-called superior pulmonary sulcus tumor. Apparently the osteoarthropathy reached considerable dimensions when the neoplasm was still small. In two hospitals where the patient was observed prior to his entry to the Montefiore Hospital the "veiling" of the apex was identified as tuberculous and not carcinomatous. There was no suppuration of the lung or of the tumor at the postmortem investigation.

The appearance of the patient was that of a person with acromegaly; the face was oval and the chin strong; the hands were voluminous and spadelike and the feet were gigantic. This was due to the characteristic periosteal overgrowth as well as to the increase in size of the soft tissues, which were swollen without revealing traces of pitting edema. It is not understood why megalia cutis et ossium should make its appearance in one case and be absent in others.

Not only the extremities (ἄκρα) but the viscera as well were enlarged (μεγάλα). The patient showed a splanchnomegaly. As his weight before death was about 52 Kg., the weight of his heart (470 Gm.), spleen (430 Gm.), kidneys (620 Gm.) and adrenals (27 Gm.) should be considered as enormously increased.

Tufting of the terminal phalanges characteristic of acromegaly was present in this case too.

Finally, the pituitary gland was twice its normal size, revealing a pronounced hyperplasia of the eosinophilic cells. The testes showed atrophy of tubules, with no spermatogenesis.

CASE 2.—*History.*—A housewife of 61 years entered the Montefiore Hospital complaining of weakness and of constant pain in the lower extremities. Her husband and five children

were living and well. One child had died at the age of 5 years of croup. There had been one miscarriage at the third month of pregnancy, following a fall. Seventeen years prior to her admission, after an episode of irregular vaginal bleeding, her uterus and tubes were

Fig. 2 (case 2).—Roentgen appearance of cancer of the lower lobe of the left lung. Photograph of the patient, with redundant eyelids, macroglossia, swollen hands, clubbed fingers and hirsutism.

removed. In 1925 she underwent a perineal operation complicated by an abscess of the right lung which subsided spontaneously. In 1929 her gallbladder was removed; it was inflamed but contained no stones.

Her present illness began in the fall of 1940, with a "cold" which persisted for two months. After that a cough productive of small amounts of sputum developed. Simultaneously her appetite began to deteriorate, and soon pain in the knee joints and legs set in; her fingers commenced to show clubbing.

In February 1941 she entered a hospital, where it was noticed that "her features were heavy and her skin was coarse, dry and thick." Her fingers and toes showed a marked degree of clubbing; the nails were beak shaped. Nothing abnormal was found in the lungs. She was discharged unimproved. A few weeks later she entered the Montefiore Hospital.

Examination.—The patient was obese despite evidence of recent loss of weight. Her skin was gray and coarse. There was no apparent thinning of the eyebrows; the upper lip showed a considerable degree of hirsutism. Her tongue was noticeably enlarged (macroglossia) and its dorsum was coarsely furrowed (fig. 2). There was rounding of the shoulders, and the lips were thick. There were deep corrugations of the scalp resembling the "bulldog" scalp as described by American authors in acromegaly. It could be picked up in large folds, especially around the occipital region. (It could not be photographed because of the growth of hair on the head, which the woman refused to have removed.) Over the forehead, face and upper eyelids, too, the skin was thickened, furrowed and redundant. Forearms, hands, legs and feet were enormously enlarged. The length of the fingers was not affected, but they showed pronounced clubbing (fig. 2) and their circumferences as well as those of the hands were greatly increased. The ankles and feet were swollen, with pronounced enlargement of the feet and toes of the same character as in the upper extremities. The circumferences of various structures of the upper and of the lower extremities are shown in the table:

	Circumference, Cm.			Circumference, Cm.	
Structure	Right	Left	Structure	Right	Left
Thumb	6	6	First toe	10.75	10.50
Index finger	9.5	9.5	Second toe	6.75	7
Middle finger	9.75	9.5	Third toe	7	6.75
Ring finger	9.25	9.5	Fourth toe	6.75	6.75
Little finger	9	9	Fifth toe	6.5	6.5

The circumference of the right wrist was 20.5 cm. and of the left 19.5 cm.; of the right palm 22.25 and of the left 21. The right foot at the ankle measured 28 cm. in circumference, the left 29; the right calf measured 31.5 cm. and the left 31.5 There was extreme tenderness of the bones of the hands and wrists; also of the lower ends of the radiuses and ulnas. The outer third of the clavicle, too, was extremely tender. The neurologic examination showed no abnormalities, and a bronchoscopic study failed to reveal an endobronchial lesion.

Laboratory Data.—The basal metabolic rate was + 1 per cent. The hemoglobin content was 71 per cent. The white blood corpuscles numbered 7,200 per cubic millimeter, with a normal differential count. The urine was normal. The concentration of sugar in the blood was 123 mg. per hundred cubic centimeters of blood; of urea, 11.4 mg.; of cholesterol, 158 mg.; of calcium, 9.4 mg.; of phosphorus, 3.3 mg.; of albumin, 3.8 mg., and of globulin, 2.4. The phosphatase activity was 5.3 Bodansky units. The blood pressure was 112 systolic and 78 diastolic.

Roentgenologic Examination.—Chest: A large circular, sharply delineated mass about 3 cm. in diameter was seen extending from the left hilum (fig. 2). A lateral view revealed the mass to be situated in the midportion of the lung, probably in the upper lobe, close to the hilus.

Left Shoulder Including the Upper Two Thirds of the Humerus: There was an irregular periosteal thickening of the bone along the entire shaft of the humerus and along the outer third of the shaft of the clavicle. Hyperostotic changes were noted to involve the acromion process of the scapula, with periosteal thickening along the lateral border.

Right Shoulder: There was periosteal thickening of the bone along the outer third of the shaft of the clavicle and periosteal thickening along the medial aspect of the upper third of the shaft of the humerus and the lateral aspect of the lower third.

Hands: There were extensive deposits under the periosteum of the phalanges and metacarpal bones (fig. 3).

Left Forearm: There was irregular periosteal thickening along the shafts of both bones. The thickening was most pronounced along the upper third of the shaft of the ulna and was similar to the changes noted in the hands and feet.

Legs: Irregular periosteal thickening was observed along the shafts of both bones.

Feet: There were extensive irregular subperiosteal deposits along the shafts of all the metatarsal bones and the proximal row of phalanges (fig. 3). There was also periosteal

thickening along the medial and lateral aspects of the shafts of the femurs. The terminal phalanges of the fingers and toes showed tufting (fig. 3). The sella turcica was not enlarged, but the cranial bones were thickened.

The clinical diagnosis was acropachyderma with pachyperiostosis; tumor of the lung.

Tissue obtained by aspiration from the mass in the chest visualized with roentgen rays showed the growth to be a squamous cell carcinoma. The woman died after seven months in the hospital. Autopsy was not performed.

Comment.—While in the previous case the pulmonary cancer with Pancoast syndrome fully absorbed my initial interest (the case has been reported from this angle [4]), the appearance of this patient was so striking that the mass visualized in the lungs was relegated to a second rank and the interest was centered on the identification of the extrapulmonary condition. The two diseases were thought to be independent of each other.

Myxedema, to be sure, was the first diagnosis that came to mind. But that she had no hypothyroid disease soon became apparent from her normal basal metabolic rate, her voice, her skin and other signs.

Her general appearance strongly suggested acromegaly of the massive type (*type massif*) as opposed to the giant type (*type géant*) described by Marie. Similar to patients with

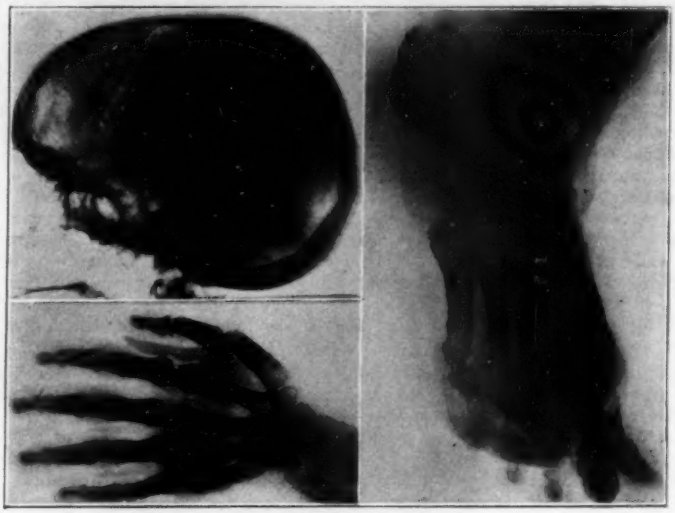

Fig. 3 (case 2).—Marked thickening of the bones of the cranial vault. Roentgen appearance of hand and foot, with extensive wartlike periostitis and tufting of terminal phalanges of fingers and toes.

acromegaly, she showed involvement of the skeleton, with the characteristic tufting of the terminal phalanges, and soft tissues. Her tongue was enlarged (macroglossia), her features coarse, her eyes puffy, her skull thickened and her scalp redundant ("bulldog" scalp).

The characteristics enumerated brought to mind another condition discussed at some length in Europe but barely touched on in America. The condition was described under various titles: cutis verticis gyrata, pachyacria, megalia cutis et ossium, pseudoacromegaly and acromegalism. Originally it was believed that the condition represented a variety of diseases until Touraine, Solente and Golé [5] produced evidence to show that in all cases the malady was the same. Golé,[6] an assistant of Touraine, abstracted most of the reported cases in a thesis entitled "Un syndrome ostéo-dermopathique; pachydermie plicaturée avec pachypériostose des extrémités." Brugsch,[7] in a report of a case thought the name "acropachyderma with pachy-

4. Fried, B. M: Am. J. Cancer **20**:791, 1934.

5. Touraine, A.; Solente, G., and Golé, L.: Presse méd. **43**:1820, 1935.

6. Golé, L.: Un syndrome ostéo-dermopathique, Thesis, Paris, Vigot frères, 1935.

7. Brugsch, H. G.: Acropachyderma with Pachyperiositis, Arch. Int. Med. **68**:687 (Oct.) 1941.

periostosis" more suitable. The malady is characterized by new deposits of periosteum around the long bones; by increase in size of the extremities (squaring); by clubbing of the fingers and toes, and by redundancy of the skin of the face and skull. In the cases reported in the literature the disease occurred in young males. It is to be stressed that it was not preceded or accompanied by any other disease of the viscera.

CASE 3.—*History.*—A childless widow of 55 years entered the hospital in September 1932, complaining of productive cough and pains in the upper and lower extremities. Early in 1930 she was affected by postprandial attacks of vomiting, which were relieved by dieting and gastric lavage. With her respiratory difficulties unabated she was admitted to a hospital, where a roentgen examination revealed a shadow occupying the mesial portion of the lower half of the upper lobe of the right lung. With the bronchoscope an infiltration of the right main bronchus extending into the upper lobe bronchus was seen. She was subjected to treatment with roentgen rays, but this was soon abandoned because of repeated hemoptyses and constant blood streaking. She was discharged from the institution unimproved.

The mild pain in the extremities which had existed for some time became aggravated, and motion became painful. She lost weight and strength. She was then hospitalized at the Montefiore Hospital.

Examination.—She appeared frail and undernourished. Her chin and upper lip were covered with a thick growth of hair. The hirsutism had appeared about one year previously, at which time her skin began to take on a brownish hue; she was never bronzed. There was considerable puffiness around her eyes, giving her a mongoloid appearance. There was a general adenopathy, and the cervical veins showed dilatation. Her extremities were massive, in contrast to her frail body, which weighed 40 Kg. The extremities throughout their entire length were thick, round and shapeless, which gave her a grotesque appearance. The hands were wide and spadelike. The distal phalanges were clubbed, and the distal portions of the radiuses and ulnas were greatly widened. There was no pitting edema.

The right hemithorax was retracted, and the trachea was deviated to this side. There was dulness to percussion, and rales were heard throughout the entire right lung; the left lung showed no abnormalities. The liver was palpable several centimeters below the costal margin, but there was no tenderness on palpation of the abdomen. The blood pressure was 160 systolic and 100 diastolic. There was a mild hypochromic anemia. The basal metabolic rate oscillated between + 18 and + 25 per cent. There was severe trismus, the separation between the upper and the lower jaw being no more than a few millimeters; the separation could be made only by force.

Roentgen Examination.—Chest: A fairly large mass, the size of a lemon, extending out from the right hilus and spreading toward the parenchyma was noticecd. The middle and lower lobes contained a few metastatic nodules, and the pleura seemed to be thickened (fig. 4).

Bones: The bones were moderately atrophic, showing extensive periosteal thickening along the entire extent of the shafts of the humeri (fig. 4). The hands revealed periosteal thickening along the metacarpal bones, the phalanges, the radiuses and ulnas (fig. 4). There was tufting of the terminal phalanges of fingers and toes.

Course.—The patient declined slowly and died after several months in the hospital.

Necropsy.—Gross Examination: The body was that of a poorly developed and considerably emaciated woman, 145 cm. in length. The skin was pale and sallow; the hair was gray, coarse and abundant. The upper eyelids were puffy, producing a mongoloid appearance. The chin and upper lip were abundantly covered with hair. All extremities showed a high degree of osteoarthropathy. The distal phalanges revealed a pronounced clubbing and the distal portions of the arms a noticeable widening.

The left lung was free from adhesions and appeared normal, while the right was firmly adherent to the chest wall. It was about one half the size of the left, its pleura measuring 5 mm. in thickness. The upper lobe was fibrous and atelectatic. At the hilus all lobes showed infiltration by a tumor mass measuring 3.5 cm. in diameter. The growth began about 1 cm. below the bifurcation and grew downward along the peribronchial tissue, virtually enveloping the bronchi. The right main artery was surrounded by the greatly thickened pleura, which was infiltrated by tumor so that its lumen was narrowed. The superior vena cava, too, was encircled by the thick pleura, which distorted its course and narrowed its lumen. The tracheobronchial lymph nodes were invaded by tumor. The heart, liver, kidneys and spleen were normal in appearance. The left adrenal gland showed a cortical adenoma measuring 0.5 cm. in diameter. The thyroid showed several adenomas. The uterus contained myomas, and the ovaries were small and fibrous. The brain, the pituitary body and the pineal gland were seemingly normal. The anatomic diagnoses were: bronchiogenic carcinoma on the

right side with metastases to the left lung, the left kidney, the spleen and the vertebral column; hirsutism; cortical adenoma of the left adrenal; adenoma of the thyroid; myoma of the uterus; diffuse pulmonary osteoarthropathy.

Microscopic Examination: Histologically the tumor was a stratified squamous epithelial carcinoma. The diseased lung showed wide areas of fibrosis due apparently to radiation

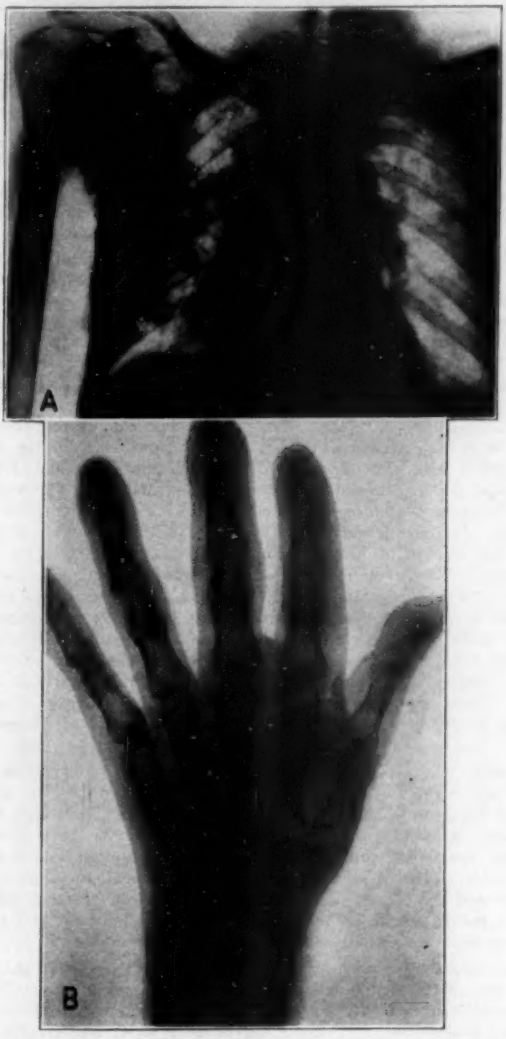

Fig. 4 (case 3).—*A*, cancer of the lower lobe of the right lung. The right humerus shows periosteal overgrowth. *B*, roentgen appearance of the left hand, with periostitis of the phalanges, ulna and radius and some atrophy of bones and tufting of the terminal phalanges.

therapy. The thyroid showed a moderate degree of colloid goiter and several adenomas. The adrenals, too, showed a sizable adenoma. In the pituitary there was hyperplasia of the cells of the anterior lobe with eosinophilic elements in the majority.

Comment.—In this case the tumor took origin in the mucosa of the right main bronchus, forming a relatively small mass at the hilus of the lung. The fibrosis and shrinkage of the pulmonary tissue were due to the radiation therapy rather than to the neoplasm, culminating in the mutilation of the bronchi and blood vessels.

As in other cases of this group the megalia cutis et ossium became manifest clinically prior to that of the malignant new growth. As in the other cases, too, this aspect of the disease was merely recorded and otherwise was neglected.

The consensus was that the woman had myxedema in addition to her pulmonary cancer. It is of interest that whereas carcinoma rarely develops in a patient with hyperthyroidism its occurrence in a patient with hypothyroidism (myxedema) is not uncommon. At necropsy one adrenal and the thyroid showed sizable adenomas and the pituitary showed hyperplasia of the oxyphilic cells.

Case 4.—*History.*—A manual laborer 41 years of age, whose wife and 17 year old daughter were in good health, was admitted to the Montefiore Hospital in March 1937. His father, a sufferer from asthma for many years, had died at 65 years of a cause unknown to the patient. His mother had died at the age of 32 years after a miscarriage. Ten stepbrothers and stepsisters were in good health.

The onset of illness dated back to the latter part of 1935. It started with painful swelling involving successively the ankles, knees, upper extremities and shoulder joints. From April to October 1936, he was under observation successively in three hospitals. The report of the diagnosis in the first hospital (October 1936) read as follows:

The lungs and the heart showed no abnormalities. The upper extremities showed limitation of and pain in all joints on motion. The wrists and elbows were swollen and warm. The hands were considerably enlarged and swollen, as were the proximal interphalangeal joints. The knees, ankles and feet, too, were hot and tender on motion; motion was limited. The feet were considerably enlarged. There was marked swelling of the breast. Bronchoscopic examination failed to reveal abnormalities, but an aspiration biopsy of the lung revealed tumor tissue which suggested metastatic carcinoma. The Wassermann and Kahn reactions were negative, and the exudate from the joints showed no abnormalities. The patient was discharged from the hospital after two and one half months. Two weeks later he was readmitted to the same institution. In the interval he had gained 2 Kg. in weight, but a productive cough, small hemoptyses and dull pain in the right hemithorax had developed. Pain in the knee joints became aggravated and their motion more restricted. His temperature averaged 101.5 F. His features were coarse; his breasts were considerably enlarged and the extremities were massive. The pain in the joints was so severe that large doses of sedatives were required to afford minimal relief. In the right lung there was an area of dulness; bronchovesicular breathing, decreased vocal fremitus and moist rales were found anteriorly between the fourth and the sixth ribs. On roentgen examination the shadow in the right lung visualized previously was now larger. There was loss of normal tapering of forearms. The erythrocyte sedimentation rate was 55 per cent. He was discharged and shortly after entered the Montefiore Hospital

Gross Examination.—At Montefiore Hospital the following observations on admission were recorded: There was evidence of considerable loss of weight. The joints of the hands, shoulders, feet and knees were severely swollen and painful. The lower limbs were massive, clumsy and shapeless. The tibias showed anterior bowing (fig. 5). The hands were particularly striking, resembling spades or paddles with the fingers showing pronounced clubbing (figs. 5 and 6). The joints of the knees and ankles contained small amounts of fluid. There was general adenopathy and gynecomastia. The lower two thirds of the right lung were dull to percussion, and the breath sounds in this area were barely audible. His features were coarse and the color of the skin somewhat bronzed, though not pigmented.

Roentgen Examination of Bones.—There was an enormous periosteal reaction with bone production about the shafts of the femurs, tibias, fibulas and metacarpal bones. There was extreme thickening and irregularity of the periosteum along the shafts of the humeri, ulnas, radiuses, tibias and fibulas (fig. 5). In the pelvis there were hypertrophic changes along both iliums and femurs. The sella turcica was large, but there were no evidences of destruction.

Bronchoscopic Examination.—Bronchoscopic examination revealed a large friable mass completely occluding the bronchus of the lower lobe of the right lung below the apical branch.

Diagnosis.—The clinical diagnoses were: bronchiogenic carcinoma of the right lung; chronic pulmonary osteoarthropathy; endocrinopathy.

Course.—The patient died after five months in the hospital.

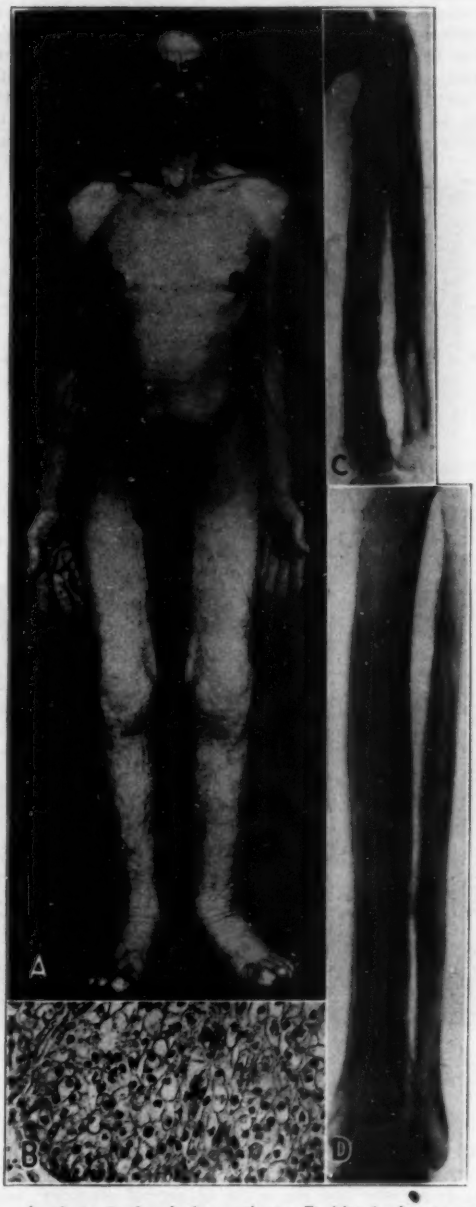

Fig. 5 (case 4).—*A*, photograph of the patient; *B*, histologic structure of the bronchial cancer; *C*, roentgen appearance of the ulna and radius; *D*, tibia and fibula with extensive periosteal overgrowth.

Necropsy.—The body was that of a well developed and moderately emaciated man. The features were coarse, and the mandibulum was prognathic. The hands were spadelike, with sausage-like, clubbed fingers. The left tibia was slightly curved anteriorly and was thicker than the right. Both were extremely swollen and shapeless, showing, however, an insignificant degree of edema. The feet were large and flat, and the toes were clubbed. The pleural cavities showed no fluid. The pleura of the left lung was smooth, and the lung showed no gross changes. The right lung was adherent to the wall of the chest and the diaphragm. The lower lobe of the lung was voluminous and firm. A tumor measuring 8 cm. in diameter and extending from the hilus was found in the midportion of the lobe. Apparently it arose in

Fig. 6 (case 4).—*A*, carcinoma of the lower lobe of the right lung. *B*, roentgen appearance of the left hand, showing lamellary periostitis. *C*, photograph of the right hand, with clubbed fingers.

the mucosa of a small bronchus and spread in a fanlike shape toward the periphery. It was soft, lobulated, hemorrhagic and partly necrotic. The large vessels and bronchi were patent. The heart was of moderate size and the aorta of normal elasticity, with a few plaques of atherosclerosis. The coronary arteries were patent. The liver was normal, but the spleen was slightly enlarged and firmer than usual. Other abdominal viscera showed no deviation from normal, except for the adrenals, which showed several cortical adenomas. The thyroid showed no abnormalities, but the anterior lobe of the pituitary was rather prominent. The genitalia were normal on gross examination.

Microscopically the tumor was made up of large polygonal cells with a sharply delimited clear cytoplasm and an eccentric nucleus rich in chromatin. The cells were gathered in large nests separated by fine fibrous partitions containing small clefts filled with red cells (fig. 5). Mitotic figures were common. Necroses and hemorrhages were common throughout the new growth. Areas of typical squamous carcinoma alternated with another type, described by some European pathologists as paramalpighian. In the metastases the new growth was diffusely of the paramalpighian variety. Other viscera, except for the spleen, which showed amyloid, were within normal limits. The pituitary showed hypertrophy and hyperplasia of the eosinophilic cells of the anterior lobe.

Comment.—Continental physicians disputed Marie's contention that the bones as well as the joints are involved in the process. They were opposed to the term *osteoarthropathy*. Although pathologic changes were not found in the joints of this patient, clinically they all showed swelling, exudate and exquisite soreness.

The osteoarthropathy in this case, as in other cases of this series, manifested itself clinically before the pulmonary disease became evident. Its progress was rapid and stormy. It was attributed to an endocrine disturbance the nature of which was not understood.

The pulmonary circulation showed no deviation from the normal. The adrenals showed several adenomas; the thyroid was above the average weight; the pituitary, too, was enlarged and under the microscope showed hyperplasia of the oxyphilic cells.

COMMENT

The pathogenesis of diffuse osteoarthropathy occurring in chronic pulmonary diseases is as obscure today as it was when Marie first described it. The conception of Pigeaux,[1] postulated in 1832 for clubbed fingers, is thought to hold equally true for the disease as seen in the patients herein presented. Pigeaux stated: "Three years of investigation have shown that the formation of curved nails is influenced by embarrassment in respiration and circulation; generally it occurs in all conditions affecting 'hematosis.'" Marie in his original paper attributed the symptom complex to the selective absorption of toxins from the affected lung. Crump,[8] from Erdheim's laboratory, stated: "There is an abnormal substance circulating in the blood which affects the periost, the bones, the joints and the soft parts of the terminal phalanges, as evidenced by clubbing of the fingers." It may be seen that the soft parts are affected not only in the phalanges but in the limbs throughout their entire length.

Before presenting the discussion on the problem of the nature of this phenomenon it is desirable to review briefly its pathologic anatomy.

Observations indicate that not all bones are affected with equal intensity. The tibia and humerus are more intensely involved than other bones, and in the same bone the lesion is more severely developed in the diaphysis than in the epiphysis. As in all diseases of the skeletal system, the process involves both the bone and the periosteum. In the former, new bone formation (hyperostosis) is seen here and there. The picture, however, is dominated by osteoporosis; there is thinning out of the corticalis and the compacta. In the periost it manifests itself as a periostitis (osteophytosis).

The periost is normally composed of dense fibrous tissue. Whenever formation of new bone is called for and whenever there is destruction of bone a new layer, the cambium, is formed on the inner surface of the preexisting periost. The cambium differs from the old periosteal layer in its poorer content of reticulum fibers, of cellular elements and of blood vessels. The cambium, and not the original periost, serves as matrix for newly formed bone. The intimate mechanism of the transformation of the cambium into bone is not understood. It may be ushered

8. Crump, C.: Virchows Arch. f. path. Anat. **271**:467, 1929.

in by local or by general conditions, by action of microbes (syphilis, osteomyelitis) or by a general disturbance, as in the cases herein presented. It may be localized, or it may be diffuse.

By studying different parts of the bone one finds different stages of the process, which has enabled investigators to reconstruct the life history of the disease. Thus it was established that the new periost is formed layer by layer, the new layer being superimposed on the one already existing, which gives to the newly formed structure a lamellary appearance visualized with the roentgen rays. Usually the new periost envelops the bone as the bark envelops a tree, its surface having a porous or wartlike appearance (figs. 1, 3, 4, 5 and 6). It is significant that osteoporosis is also present in bones and in areas of bones where no new periosteum was formed. It is, then, even possible that the disease originates primarily not in the periosteum, as is almost universally believed, but in the bones. However that may be, the process is that of a hyperplastic porotic osteoperiostitis. As a result, the bones are considerably thickened and disfigured; they are not elongated.

Not only the bones but the soft tissues as well are involved. There occurs a considerable thickening of the skin and subcutaneous tissue of the hands and feet, which produces the characteristic appearance of the extremities in chronic pulmonary osteoarthropathy. There is, then, a megalia cutis et ossium. The skin is soft and doughy but shows no pitting edema.

Hitherto pathologic changes of the nature described were said to be present uniquely in osteoarthropathies, occurring in tumors (primary or metastatic) and in certain chronic purulent conditions of the lungs.

In the comment to case 2 attention was drawn to a new entity isolated by French clinicians (Touraine and Golé) under the name of *pachydermie plicaturée avec pachypériostose des extrémités*. Patients affected with this malady show characteristic clubbing of the fingers and toes, squaring of the extremities, thickening of the skin and deformities of the long bones with lamellary deposits of periost. Differing in some details from pulmonary osteoarthropathy, the condition is, on the whole, an exact counterpart of that in the cases herein presented. The pathologic and roentgenologic similarities of the skeletal and cutaneous systems in the two diseases are identical to the finest details. In a case recently reported by Brugsch [7] the similarities were striking. It is particularly significant that the malady does not develop on the basis of a cardiorespiratory or other visceral disease. The consensus is that the disease in these patients is of endocrine origin.

Prior to the isolation of this symptom complex by Touraine and co-workers cases of this condition were reported under the designation of pseudoacromegaly or acromegalism, because of their close resemblance to acromegaly, the endocrine origin of which is today firmly established.

It is well to stress that in acromegaly, as in pulmonary osteoarthropathy, the bones are not elongated, their increase in size being due to the increase of both the periosteal and the subcutaneous tissues. Microscopically, too, the structural changes in the two diseases are closely related. The tufting of the terminal phalanges of fingers and toes, regarded by Cushing and others as an osteologic sign pathognomonic of acromegaly, is likewise present in the disease described by Touraine as well as in pulmonary osteoarthropathy. Tufting of the terminal phalanges of fingers and toes was pronounced in all 4 of my patients. Generally the process in the three diseases affects the same system, the mesoderm. The pathologic changes may vary in degree, and their advance may differ in tempo, but qualitatively they are essentially of the same nature.

The difficulties in the differential diagnosis between pulmonary osteoarthropathy, pachydermia with pachyperiostosis and acromegaly is demonstrated in the case of the Hagner brothers. In 1868 their disease was defined by Friedrich [9] as hyperostosis of the entire skeleton. In 1888 Erb identified their disease as acromegaly. Marie, too, at first interpreted the condition as acromegaly but subsequently changed his interpretation to pulmonary osteoarthropathy. In 1899 Sternberg [10] stated that the disease of the Hagners was distinct both from acromegaly and from osteoarthropathy. At present it is included in the group of pachydermia with pachyperiostosis.

The foregoing facts and the data obtained from the study of the cases here reported favor the conception that diffuse osteoarthropathy found in neoplastic diseases of the lungs is in all probability caused not by toxins (*miasmata imaginaria*, to use Osler's expression) or by circulatory disturbances, as postulated more than a century ago, but by an endocrine imbalance akin to acromegaly and to pachydermia with pachyperiostosis.

Regrettably, cases of chronic pulmonary osteoarthropathy hitherto reported in the literature (numbering about 100) have never been studied from this angle. Attention was generally drawn to the bones and the lungs, while metabolic and endocrine possibilities were totally ignored. Clinicians never went beyond Pigeaux's and Marie's hypotheses. Apropos of a case of this kind which I observed in 1928 I wrote: [11] ". . . His appearance was most impressive, resembling somewhat, that of an acromegalic. His features were rather large and disproportionate and the joints looked as if there was a subluxation. The lower jaw was prominent . . ."

An analysis of the 4 cases here reported (deficient though their study may be from an endocrinologic point of view) revealed data pointing toward the conception that the megalia cutis et ossium resulted in all probability from a disturbance in the function of the organs of internal secretion. Summarily the data are: in case 1 acromegalic appearance of the patient, tufting of the terminal phalanges of the fingers and toes; splanchnomegaly, atrophy of the testicles and a large adenohypophysis showing pronounced hyperplasia of eosinophilic elements; in case 2 acromegalic appearance of the patient, "bulldog" scalp, hirsutism, macroglossia, tufting of the terminal phalanges of the fingers and toes and thickening of cranial vault; in case 3 mongoloid features of the patient, secondary male characteristics, large cortical adenoma of the adrenals, several adenomas of the thyroid and hyperplasia of cells of the anterior lobe of the pituitary, with eosinophilic cells in the majority; in case 4 coarse acromegalic features, gynecomastia, several cortical adenomas of the adrenals, roentgenologic evidence of enlargement of the sella turcica and tufting of the terminal phalanges of the fingers and toes.

That the lungs are endowed with functions in addition to respiration has been stressed on many occasions. Various writers have attributed to the lungs a role in the metabolism of lipids. This was suggested by the fact that absorbed albumins and carbohydrates pass directly into the liver while fatty substances are transported by way of the lymphatics and the thoracic duct to the right side of the heart and to the lungs. Fort,[12] in 1867, suggested that the lungs are

9. Friedrich, N.: Virchows Arch. f. path. Anat. **43**:63, 1868.

10. Sternberg, M.: Acromegaly, London, New Sydenham Society, 1899.

11. Fried, B. M.: Primary Carcinoma of the Lungs, Baltimore, Williams & Wilkins Company, 1932, p. 117.

12. Fort, A. J. A.: Anatomie et physiologie du poumon considéré comme organ de sécrétion, Paris, A. Delahaye, 1867.

characteristically secretory organs, and he used the term *la glande pulmonaire*—the pulmonary gland. In recent years Roger [13] and his associates, Aschoff [14] and others [15] have subscribed to this conception.

Apparently the functions of the lungs are multiple, and their interrelation with other organs, particularly of internal secretion, is complex and worthy of further study.

As to the interdependence of tumors of the lungs and the organs of internal secretion no information is available, to my knowledge.

SUMMARY

Four cases of chronic pulmonary osteoarthropathy in patients with bronchiogenic cancer are reported. Evidence is produced to show that the condition is in all likelihood caused by an endocrine imbalance (dyspituitarism).

125 West Seventy-Sixth Street.

13. Roger, G. H., and Binet, L.: Rev. de méd. **42**:1, 1925.
14. Aschoff, L.: Ztschr. f. d. ges. exper. Med. **50**:52, 1926.
15. Fried, B. M.: Defensive and Metabolic Apparatus of Lungs, Arch. Path. **6**:1008 (Dec.) 1928; Lungs and Macrophage System, ibid. **17**:76 (Jan.) 1934.

PREPARATION OF SYNTHETIC IMMUNE SERUM AND NATURE OF IMMUNITY

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Prior to the work of Woehler, who synthesized urea more than a century ago, vital processes and products were considered inseparable from the living body, and the doctrine of vitalism proclaimed them forever beyond the poor power of mankind to understand or reproduce. The tiny crack produced by Woehler in the structure was enlarged by many others, and vitalism is long since defunct. Among the ruins, however, there remains hidden certain knowledge which still awaits excavation. It is with such a fragment, namely the enigma of immunity, that this report is concerned.

THEORY

It has long been recognized that antibodies are carried in close association with the globulin fraction of the blood plasma. While certain workers, notably Huntoon [1] and Olitzki and Frankel,[2] attempted to separate them from all protein substances, others considered that this is impossible and accepted the belief that they are themselves globulins of a specialized form. In the past decade this viewpoint has been adopted by a great majority of investigators. Felton [3] was among the first to voice this conviction, and many others have followed his lead.

In the past proteins have been separated by precipitation with increasing concentrations of a salt and classified on this basis. The antitoxic serums, such as that used in diphtheria, have been found associated with the pseudoglobulin, a fraction which is carried down by a 50 per cent saturated solution of ammonium sulfate and is capable of re-solution in pure water. Antipneumococcus and similar antibacterial serums have been extracted from the euglobulin, which is precipitated at 28 to 33 per cent saturation and requires water plus the salt for re-solution.

The more recent classification of blood proteins by electrophoresis as introduced by Tiselius has stimulated further advances. This method lists proteins according to their rate of migration through a U tube while under the influence of an electric current and offers no exact comparison to the results obtained by precipitation with ammonium sulfate. Thus Svensson [4] could demonstrate no electrochemical difference between pseudoglobulin and euglobulin. Albumin moves most rapidly and also has the smallest molecular weight and the greatest osmotic pressure. It is followed by the progressively slower alpha, beta and gamma globulins with decreasing osmotic pressures and increasing molecular weights.

1. Huntoon, F. M.: Pneumococcus Antibody Solution, J. Lab. & Clin. Med. **11**:759-762 (May) 1926.

2. Olitzki, L., and Frankel, M.: Absorption and Elution of Antibodies from Various Antisera, Proc. Soc. Exper. Biol. & Med. **28**:492-494 (Feb.) 1931. Frankel, M.: Method of Separating Antibodies from Serum Proteins: Investigation on Protein-Free Antibody, Proc. Roy. Soc., London, s.B **111**:165-174 (July 1) 1932.

3. Felton, L. D.: Pneumococcus Antibodies—What Are They? Science **79**:277-279 (March 23) 1934.

4. Svensson, H.: Fractionation of Serum with Ammonium Sulfate and Water Dialysis Studied by Electrophoresis, J. Biol. Chem. **139**:805-815 (June) 1941.

Kabat [5] observed that in the horse, cow and pig antibody molecules are extremely heavy, having molecular weights of about 990,000. In the human subject, the monkey and the rabbit, antibody molecules were of regular gamma globulin weight. In certain horses after long immunization he observed smaller antibodies of lesser weight which appeared among the heavier molecules. Kekwick [6] discovered that both beta and gamma globulins contained antitoxic molecules. Antitetanic serum held about 50 per cent in the gamma fraction, Anti-Clostridium-welchii serum 25 per cent and antidiphtheritic serum about 10 per cent. In anti-pneumococcus serum a new T fraction moving between beta and gamma globulins has been described as the location of the antibodies. Van der Scheer, Wyckoff and Clarke [7] found this true in some instances, while in other animals the gamma fraction contained the increased protective substances. Van der Scheer, Lagsdin and Wyckoff [8] in a later communication reported that antibody activity occurred only in the gamma globulin, with one exception. In this instance blood from a newly immunized horse contained antibodies in fraction T′ intermediate between T globulin and gamma globulin. They suggest that with prolonged immunization this fraction might not persist.

Pappenheimer, Lundgren and Williams [9] found the molecular weight of diphtheria toxin to be 70,000 and of the antitoxin 150,000.

Marrack [10] summarized the work of numerous workers to report other observations on the dimensions, shape and actions of antibodies. Some of these observations are unverified, and a few are contradictory.

Rosenau [11] stated of antibodies that "They are not necessarily 'bodies' but may be colloidal or physical states of the blood or other body fluids."

Little of a positive nature is known regarding the site and mode of origin of antibodies. Certain theorists hold that they develop in the fixed cells of the body and are then poured out into the blood and lymph. The lymph glands, the spleen and the reticuloendothelial system have been variously named as the place where production occurs, but convincing evidence is lacking in almost every instance. Sabin [12] stated the modern concept from this viewpoint. It is to be noted that certain of her conclusions are inferred rather than taken as proved facts. Cannon [13] also assumed that antibodies arise in the fixed cells of the reticuloendothelial system. Others have maintained the so-called humoral theory, i. e., that antibodies are formed in the blood and that the circulatory system is the reservoir. Ehrlich's

5. Kabat, E. A.: The Molecular Weight of Antibodies, J. Exper. Med. **69**:103-118 (Jan.) 1939.

6. Kekwick, R. A.: Constitution of Some Antitoxic Horse Sera, Chem. & Indust. **60**:486 (June 28) 1941.

7. van der Scheer, J.; Wyckoff, R. W. G., and Clarke, F. H.: Electrophoretic Analysis of Several Hyperimmune Horse Sera, J. Immunol. **39**:65-71 (July) 1940.

8. van der Scheer, J.; Lagsdin, J. B., and Wyckoff, R. W. G.: Electrophoretic and Ultracentrifugal Analysis of Antipneumococcal Horse Sera, J. Immunol. **41**:209-223 (June) 1941.

9. Pappenheimer, A. M.; Lundgren, H. P., and Williams, J. W.: Studies on the Molecular Weight of Diphtheria Toxin, Antitoxin and Their Reaction Products, J. Exper. Med. **71**: 247-262 (Feb.) 1940.

10. Marrack, J. R.: Immunochemistry, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1942, vol. 11, pp. 629-654.

11. Rosenau, M. J.: Preventive Medicine and Hygiene, ed. 6, New York, D. Appleton-Century Company, Inc., 1935, p. 643.

12. Sabin, F. R.: Cellular Reactions to a Dye-Protein with a Concept of the Mechanism of Antibody Formation, J. Exper. Med. **70**:67-82 (July) 1939.

13. Cannon, P. R.: Antibodies and the Protein Reserves, J. Immunol. **44**:107-114 (June) 1942.

theory sought to explain the process as an intracellular development but has been practically discarded as inadequate to explain the known facts. Many terms introduced by Ehrlich, however, are still in use. It may well be that antibodies of different classifications arise from different sources.

Concerning specificity, there is no doubt whatever that many immune serums neutralize one specific antigen and no others. Diphtheria antitoxin, first prepared by von Behring, is the prototype. Antipneumococcus serum is to be listed here and is specific for the polysaccharide hapten groups found in the pneumococcus. Heidelberger [14] has discussed these quite fully. Antimeningococcus and other serums may also be listed. It is to be noted that specific antibodies of these types are frequently absent in human beings and animals who have not been exposed to the corresponding infection.

To produce active immunity or therapeutic serum it is usually necessary to stimulate the biologic production by repeated injections of antigen over a period of weeks and often months. Even the results from single doses of alum-precipitated toxoid, the newest and most approved form of immunization to diphtheria, require six weeks or more to mature. The mechanisms responsible seem to be definitely specific and require a lengthy period in which to act. When undeveloped they are powerless in the face of sudden overwhelming attack.

There is, however, a different series of protective reactions which comes into activity whenever any infection gains a foothold and in certain noninfectious conditions. This is the familiar sequence of fever and increase of the white cells of the blood, which can and does become operative within a few hours after the onset of infection. It occurs in a wide variety of diseases of bacterial origin, in diphtheria, pneumonia and epidemic meningitis, all of which have been listed as amenable to treatment by specific antiserums, and in addition, in influenza, the acute exanthems and various streptococcic and staphylococcic infections, as well as in the great epidemic diseases Asiatic cholera and plague. Typhoid, typhus and yellow fevers show the thermal change but present irregularities in the action of the white blood cells.

Bacterial infection is also followed by certain chemical changes which have not been thoroughly understood. First, there is an increased metabolism of protein, which, if the end products are not properly eliminated, may produce a striking rise in the nonprotein nitrogen bodies of the blood. This has been noted by Tileston and Comfort,[15] Wakeman and Morrell,[16] Guyer and Lepkovsky,[17] Linton [18] and others. Second, there occurs a shift in the ratio of the blood proteins to one another. The fibrinogen and globulin increase, and the albumin diminishes, with a resultant decrease in the total protein, which produces definite alterations in the albumin-globulin and globulin-fibrinogen ratios. This has been

14. Heidelberger, M.: Immunochemistry, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1935, vol. 4, pp. 569-586.

15. Tileston, W., and Comfort, C. W., Jr.: The Total Non-Protein Nitrogen and the Urea of the Blood in Health and Disease as Estimated by Folin's Method, Arch. Int. Med. **14**:620-649 (Nov.) 1914.

16. Wakeman, A. M., and Morrell, C. A.: Chemistry and Metabolism in Experimental Yellow Fever in Macacus Rhesus Monkeys: Concentration of Nonprotein Nitrogenous Constituents in Experimental Yellow Fever in Macacus Rhesus Monkeys, Arch. Int. Med. **46**:290-305 (Aug.) 1930.

17. Guyer, M. F., and Lepkovsky, S.: Immunization and the Nitrogenous Constituents of the Blood, J. Immunol. **16**:175-208 (March) 1929.

18. Linton, R. W.: Blood Chemical Changes in Experimental Streptococcus Septicaemia, J. Exper. Med. **54**:223-231 (Aug.) 1931.

commented on by Hurwitz and Meyer,[19] Hurwitz and Whipple,[20] Wiener and Wiener,[21] Lovett,[22] Rowe,[23] Schoch,[24] Starlinger [25] and others.

These phenomena of fever, leukocytosis, changes in the nonprotein nitrogen content of the blood and protein alteration are purely nonspecific and appear in many infections. After a few hours or days soluble immune bodies appear in the blood, and if they are sufficiently potent, recovery with eradication of the infection may be anticipated. The crisis of pneumonia, the lysis of typhoid and other phenomena of recovery are due, at least in part, to those antibodies, whose presence may be proved by appropriate serologic and biologic methods but of whose nature and point of origin nothing is known. They are considered to be an important factor in native or natural immunity.

It is now necessary to make a seeming digression to certain purely experimental data. Balcar, Sansum and Woodyatt [26] found that by the intravenous injection of a concentrated solution of dextrose or sodium chloride into experimental animals, a diuresis could be caused which in a few hours eliminated fluid greatly in excess of that injected. When the output of fluid exceeded the intake by 25 cc. or more per kilogram of body weight there occurred a substantial rise in the body temperature, often accompanied by a chill. On the basis of these facts they proposed a so-called dehydration theory of fever according to which the water content of the body was considered to exist in two different states of colloidal combination: first, "free" or uncombined, in which condition it was available to absorb and transport heat to the skin for radiation, to act as a solvent and to perform other functions and, second, "bound" as a hydrate in various organs and tissues of the body, a physicochemical state which prevented its usefulness as a solvent and a vehicle for heat transportation. They conceived of infection as a process which greatly increased the hydration capacity of the body colloids and enabled them to combine with a major portion of the "free" water. The resulting shortage, which prevented absorption and transportation of heat energy, they held responsible for the appearance of fever. That there are increased demands for water during severe febrile illness is shown clinically by the insatiable thirst of the patient and the increased volume of fluid eliminated through the sweat and urine when recovery has come and it is no longer needed. Experimentally many observers have found concentration of the blood and other body fluids during fever.

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19. Hurwitz, S. H., and Meyer, K. F.: The Serum-Globulins in Infection and Immunity, J. Exper. Med. **24**:515-546 (Nov.) 1916.

20. Hurwitz, S. H., and Whipple, G.: The Albumin-Globulin Ratio in Experimental Intoxications and Infection, J. Exper. Med. **25**:231-253 (Feb.) 1917.

21. Wiener, H. J., and Wiener, R. E.: Plasma Proteins, Arch. Int. Med. **46**:236-265 (Aug.) 1930.

22. Lovett, B. R.: Quantitative Relation of Serum Albumin and Globulin, Arch. Path. **4**:984-1024 (Dec.) 1927.

23. Rowe, A. H.: Albumin and Globulin Content of Human Blood Serum, Arch. Int. Med. **18**:455-473 (Oct.) 1916.

24. Schoch, A.: Ueber Eiweiss-schwankungen im Blutserum bei akuten Infektionskrankheiten, Schweiz. med. Wchnschr. **56**:1017-1022 (Oct. 23) 1926.

25. Starlinger, W.: Ueber das Verhalten der zirkulierenden Eiweisskörper des menschlichen Plasmas unter normalen und krankhaften Bedingungen, Deutsche med. Wchnschr. **54**:731-733 (May 4) 1928.

26. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and the Water Reserve of the Body, Arch. Int. Med. **24**:116-128 (July) 1919.

My associates and I,[27] having occasion to repeat certain of these experiments, found that dehydration caused an increase of protein catabolism and an abnormally large accumulation of nitrogenous debris in the blood of the laboratory animals. It was then necessary to add to the dehydration theory that shortage of water causes a retention of the waste nitrogen, with the development of blood concentrations which sometimes rise to uremic heights. Such heat as is produced at this time is subject to the influences discussed by Balcar, Sansum and Woodyatt.

It was later shown [28] that in animals subjected to dehydration there occurred a rise of the leukocytes similar to that observed in infection.

The point toward which this discussion of somewhat parallel clinical and experimental observations has been directed, and the reason for the preparation of this paper has now been reached. It may be stated thus: Infection generates a biologic reaction which includes (1) fever, (2) leukocytes, (3) changes in the rate of protein disintegration and the levels of waste nitrogen accumulation in the blood, (4) alteration in plasma protein ratios, and (5) the formation of soluble immune bodies. Is it possible, then, that dehydration, which may bring about the first three conditions, is also responsible for the fourth and could be used as a method for production of the fifth? In other words, is it possible to use this method to change the preparation of immune serums from a biologic to a physiochemical problem and so to remove it from the animal body into the test tube?

I [29] have called attention to effects often obtained by the treatment of severe infections with blood transfusion wherein fresh compatible blood seemed to carry certain raw materials into the patient's blood stream. These raw materials appeared, after due intravital processing, to emerge as antibodies which exerted a favorable influence on the course of the disease. Proof that such a change actually takes place would lend strength to the claims advanced by the advocates of the humoral theory of immunity. If the transformation could be reproduced under proper control in the chemical laboratory, such an introduction of new methods into the study of immune phenomena might conceivably result in definite advances in therapy.

Recent developments suggest that production of antibodies under laboratory conditions is already within our grasp. In the early days of the century Moll [30] attempted to convert albumin into globulin by treatment with gentle heat and alkalis and found certain globulin-like properties in the product. His critics, however, pointed out that the amino acid composition was not correct, and the procedure soon ceased to have interest. Today it would be said that he had produced a denaturation of the protein.

Recently Pauling and Campbell [31] published an epoch-making report. They studied the results of denaturation of protein in the presence of an antigen and found that it opens the way to the preparation, in vitro, of specific antiserums. Using purified globulin, they observed that treatment with alkalis in varying concentrations up to p_H 11.0 caused the protein molecules to "uncoil" and take

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29. Bacon, D. K.: Blood Transfusion in the Treatment of Sepsis, Minnesota Med. **18**: 30-34 (Jan.) 1935.

30. Moll, L.: Ueber künstliche Umwandlung von Albumin in Globulin, Beitr. z. chem. Phys. u. Path. **4**:563-577, 1903.

31. Pauling, L., and Campbell, D. H.: The Manufacture of Antibodies in Vitro, J. Exper. Med. **76**:211-220 (Aug.) 1942.

the imprint of various dyestuff antigens. After renaturation by restoration of a normal p_H value there remains a configuration of the globulin molecule which enables it to combine with the antigen and act to neutralize it. Similarly, using heat denaturation, at a temperature of 57 C., they have prepared antibodies specific to pneumococcus polysaccharide which will after renaturation precipitate further increments of the polysaccharide. Thus the flexibility of the globulin molecule is advanced as a prime factor in combating various bacterial poisons, and denaturation, at least of some types, is shown not as a laboratory curiosity but as a dynamic force which is of vital importance in the maintenance of health and life.

Pauling and Campbell have carried out denaturation under artificial conditions which are seemingly incompatible with life, such as a p_H of 11.0 or a temperature of 57 C. I have sought to use procedures which can more easily be visualized as acting in the living body on whole blood plasma where natural immunity is found rather than in a dilute solution of purified globulin.

If the previously mentioned dehydration theory has any merit, blood protein must be thought of as consisting of a bound water fraction closely united to the protein molecule and perhaps within the molecular framework; the water of hydration, and a free or solvent fraction which carries the body electrolytes, such as chlorides, sulfates and bicarbonates. If any process should cause a decrease in the free water while the mineral content remained constant, one might expect a rise in the concentration of salts and also, since a p_H of 7.00 is regarded as neutral and the average p_H of blood plasma is about 7.4, it seems probable that the excess alkalinity of p_H 0.4 would become concentrated in the diminishing solvent fluid and give rise to an increase of hydroxyl ion concentration and an abnormally high p_H value in this fraction.

EXPERIMENTAL DATA

Experimental work was undertaken to test this theory. Citrated beef blood was obtained through Swift and Company at South St. Paul. It contained sulfanilamide as a preservative. It was separated by centrifugation, and the clear plasma was obtained. The p_H values were immediately determined by electrometric readings. Since no precautions were taken to prevent the escape of carbon dioxide, values ranged from p_H 7.45 to p_H 7.58, which is a trifle more alkaline than the average reading on blood collected under oil to retain the gas.

The plasma was then subjected to dehydration by the method of Flosdorf and Mudd.[32] The apparatus consists, in essence, of a closed flask containing plasma, a cold chamber surrounded by solid carbon dioxide to collect the fluid which is withdrawn and a vacuum pump to exhaust the system and extract water from the plasma. The entire system is connected by pressure-resistant tubing. It is a method commonly used to dry and preserve plasma for later use in transfusion. While Flosdorf and Mudd have devised later methods with different agents for absorption of the extracted water which are used for mass production of dried plasma, the original method proved satisfactory for the purpose of this study. Methods which require the spraying of plasma into a heated vacuum chamber were considered unsuitable and were not employed.

When the pump is first started, the air is rapidly exhausted from the plasma flask, and a violent boiling of the contents results. At this point it is necessary to admit small amounts of air to prevent entrance of the foam into the tubing. After a few minutes, when the dissolved gases, such as carbon dioxide and oxygen,

32. Flosdorf, E. W., and Mudd, S.: Procedure and Apparatus for Preservation in "Lyophile" Form of Serum and Other Biological Substances, J. Immunol. **29**:389-425 (Nov.) 1935.

have been extracted and the heavier water vapor begins to pass over, the process becomes much more quiet and may be left to progress to completion with little further attention.

This process was carried out on a number of samples of plasma to note the effect of dehydration. Estimations of the p_H were made before starting and were repeated at the end of the violent boiling period, which consumes about ten minutes, in order to note the effect of the withdrawal of carbon dioxide. A third estimation was made after about fourteen hours, when the fluid was almost dry but still mushy enough to make a good contact with the glass electrode. The last values, of course, would be slightly less than the value for dry plasma, which cannot be easily taken. The readings are given in the accompanying table.

Reference to this table will show that dehydration causes a considerable rise in the alkalinity of plasma. True, this has not been observed in the blood of living animals, but if electrodes could be fashioned to take readings in the ultramicroscopic free water fractions of plasma and not be influenced by the neighboring bound water molecules, increased alkalinity might be found. It would be a condition of great

Results of Dehydration on p_H of Blood Plasma

Specimen	1 p_H Before Treatment	2 p_H After 10 Minutes	3 p_H at Near Dryness
1	7.52	7.64	8.54
2	7.55	7.68	8.70
3	7.45	7.60	8.45
4	7.56	7.72	9.10
5	7.50	7.68	8.32
6	7.48	7.62	8.65
7	7.50	7.65	8.50
8	7.55	7.74	8.42
9	7.54	7.70	8.54
10	7.48	7.68	7.95

It is to be noted that all values in column 3 were taken on incomplete dehydrated plasma which was still mushy enough to make a good contact with the glass electrode. The p_H of completely dried plasma would probably be 0.2 to 0.5 greater.

internal chemical stresses with sharply contrasting concentrations in physically adjacent particles. This will be commented on later.

Further specimens of plasma were dehydrated as has been described and during the process were treated with an antigen. In these experiments the flask containing the specimen was placed in the incubator with the tube connection to the vapor trap entering through the upper vent hole. This attempt to maintain body temperature was unsuccessful because of the rapid withdrawal of heat in the vaporization process, and the flask remained decidedly cold during the entire period. Consequently, after the contents were about 90 per cent dehydrated and resembled a thick, mushy syrup, the suction was removed and the air pressure in the flask was permitted to return to normal. It was then kept in the incubator for an additional twelve hours to permit completion of any chemical adjustment.

METHOD

One hundred cubic centimeters of clear citrated and centrifuged beef plasma was placed in a 1,000 cc. Erlenmeyer flask. This was fitted with a rubber stopper and connected by rigid rubber tubing to a vapor trap containing solid carbon dioxide and thence to a vacuum pump. The pump was started and allowed to run for ten to fifteen minutes with occasional small admissions of air until active foaming of the plasma had subsided The flask was then opened and 2 cc. of staphylococcus toxin added. The container was then shaken to insure thorough mixing. The toxin, obtained from the Lederle Laboratories, Inc., their no. 307H565, was stated to contain 12,000 dermonecrotic doses per cubic centimeter. The cork was replaced and the pump again started and continued for twelve to fourteen hours until near dryness

was reached. During this time the flask was agitated at intervals to assist uniform evaporation and prevent caking around the edges. The pump was then disconnected, and the atmospheric pressure in the flask was permitted to return to normal. It remained in the incubator another twelve hours.

After this sufficient distilled water was added to restore the plasma to its original volume, and both the control and the processed specimens were adjusted to p_H 7.4 with tenth-normal acetic acid. This is important, as the processed specimen is apt to be definitely alkaline in spite of the fact that no alkali has been added. It was filtered and 5 cc. pipetted into each of two test tubes; 5 cc. of unprocessed plasma from the same blood was placed in a third tube for a control; 0.5 cc. of staphylococcus toxin each was added to one processed tube and the control tube; diphtheria toxin obtained from the Minnesota State Board of Health was placed in the second processed tube as another control, 0.5 cc. being used. The three tubes were set in the incubator for twelve hours to facilitate any change that might occur. A series of such experiments was made.

A second series was carried out in which plasma was dehydrated with diphtheria toxin as an antigen and test tubes were set up containing diphtheria toxin in the unprocessed control and one tube of processed plasma. Staphylococcus toxin in the second processed tube gave another control.

RESULTS

In the series which had been dehydrated against staphylococcus toxin, tube 1, containing additional toxin from the same lot, in every instance gave a copious precipitate which after settling filled about 12 to 15 per cent of the test tube. This was presumably antigen antibody precipitate. In the two control tubes the results were strikingly different. In many instances no precipitate at all came down, while in several there was an amount just sufficient to cover the bottom of the tube after settling. There was never any question or confusion, and in every instance the processed plasma treated with homologous toxin was strikingly different from the two controls.

In the series dehydrated against diphtheria toxin, tube 1, containing a further increment of the same toxin, showed a similar but less profuse precipitate than in the staphylococcus series. About 5 to 6 per cent of the volume of the tube was occupied by antigen-antibody precipitate, while in the control tubes the results were similar to those obtained with the controls in the previous series. There was usually no precipitate, except in 2 or 3 instances in which there was a very small amount, which, however, could not be confused with that which appeared in the processed tube treated with homologous toxin. Results in this series were definite without being as spectacular as those noted in the staphylococcus series. Results may be illustrated in tabular form as follows:

Plasma Dehydrated with Staphylococcus Antigen

	Control 1	Control 2	Test
	Unprocessed plasma plus staphylococcus toxin	Processed plasma plus diphtheria toxin	Processed plasma plus staphylococcus toxin
Precipitate	— to ±	— to ±	++++

Plasma Dehydrated with Diphtheria Antigen

	Control 1	Control 2	Test
	Unprocessed plasma plus diphtheria toxin	Processed plasma plus staphylococcus toxin	Processed plasma plus diphtheria toxin
Precipitate	— to ±	— to ±	++

It will be seen that these results are comparable to the ones obtained by Pauling and Campbell and show specific precipitates obtained by the treatment of plasma which had gone through a dehydration process in the presence of an antigen with further increments of the same antigen. The faint precipitate which appeared in the control tubes in a few instances could represent preexisting antibodies acquired during the life of the animal.

COMMENT

It is possible that several different forms of immunity exist, and they may arise from as many different sources. This report deals only with the specific antibodies of the blood globulin. There may be nonspecific protective substances here in addition to the specific ones, as Street [33] and van der Scheer, Bohnel, Clarke and Wyckoff [34] have demonstrated. If so, the work of separation and classification has scarcely begun. These specific antibodies seem to be of a protective nature, and the ability to combine with and carry down antigen may identify them as precipitins. The fact that the concentration of agglutinins, in the experience of many workers, fluctuates entirely independently of curative antibody strength undoubtedly places the two in separate categories. Opsonins occupy still another niche, and according to Wright [35] their entire functional activity is in doubt.

To return to the subject of this research, evidence is offered that antibodies can be formed in the native blood plasma by methods available in the average well equipped chemical laboratory and entirely independently of any mysterious "body reaction." These methods, although carried out in vitro, approximate the chemical forces which act in the body.

At this point it will be objected that evaporation of plasma in a flask and under reduced pressure to a state of near-dryness can have little in common with any conditions which exist in the circulating blood of a living animal having a free respiratory exchange under normal atmospheric pressure. It is true that differences in degree may exist between the experimental conditions just described and the changes which are found clinically, but on closer scrutiny the differences in kind seem less final than at first glance. A reduction in the volume of free water with its solvent action concentrates the dissolved electrolytes regardless of the disposition of the fraction removed. In this instance, chemical segregation in a bound water system should have no basic difference in effect from that exerted by loss through evaporation. The free water fraction is reduced in volume and contains an increased concentration of electrolytes in either case.

In glass, this causes a considerable rise in the alkalinity of the plasma. In vivo, no alkalinity comparable with these experimental figures has ever been observed.

While life lasts, the body, by variations in the carbon dioxide tension and the action of the various buffer salts, maintains a p_H value in the blood which rarely reaches 7.55. It seems not impossible, however, that this value is deceptive and that plasma actually has no homogeneous and uniform hydrogen ion concentration but has instead two different values representing bound and free water molecules in which our indicators or electrode systems read the mean. In health, the two different values should not be far apart but should form a sensitive mechanism ready to respond to antigenic stimulation with a swelling of the protein molecule due to an increase in the amount of bound water and a decrease in the amount of free water with a rise in alkalinity, or masked alkalosis. This would produce a tension at the interfacial surfaces which might conceivably alter the form or consistency of the protein sufficiently to permit its adaptation to the contours of the antigen molecule. The result would be the formation of antibodies. After recovery and restoration of a state of normal hydration there should be a disappearance of

33. Street, J. A.: Studies on the Mechanism of Species Specific Immunity Against Pneumococcus Infection, J. Immunol. **44**:53-69 (May) 1942.

34. van der Scheer, J.; Bohnel, E.; Clarke, F. H., and Wyckoff, R. W. G.: An Electrophoretic Examination of Several Antipneumococcic Rabbit Sera, J. Immunol. **44**:165-174 (June) 1942.

35. Wright, A. E.: On the Need for Abandoning Much in Immunology That Has Been Regarded as Assured, Proc. Roy. Soc. Med. **35**:161-186 (Jan.) 1942.

the masked alkalosis and a rapid sweeping of the excess waste nitrogen through the kidneys, the new antibodies being left as sole evidence of the strain that had existed.

In order to have a more complete understanding of the processes involved in the production of fever and the development of immunity, it is necessary to begin with the work of Balcar, Sansum and Woodyatt,[26] which has already been mentioned. Since they first advanced their hypothesis of "free" and "bound" water it has attracted the interest of the biochemical world, and much time and ingenuity have been expended on investigations of the question. Gortner,[36] who independently conceived the same varying relation of water to protein, discussed the evidence at some length, and showed clearly that such a dual status of water actually exists in many vegetable proteins and in certain other nonprotein colloidal systems as well. Opinions regarding the status of water in animal protein and particularly in blood are not unanimous. Jochims [37] and others affirmed the existence of bound water, while Sunderman [38] and Greenberg and Greenberg [39] denied it. The results of their experimental work have since been challenged on technical grounds. Robinson and Parsons [40] found much water present in blood and muscle which, since it was not frozen at — 20 C. must have been bound water, Hayasida,[41] in measuring the "nonsolvent" space of blood serum, discovered that it occupies about 20 volumes per cent, with rather wide fluctuations occurring as the salt content varies, and gave added proof from a different viewpoint. There is, in addition, evidence of adsorption or binding of the chloride ion in the protein molecule, a state presumably not one of solution but one which permits the protein to come into intimate contact with the bound ion. He also called attention to the fact that exclusion of a portion of the fluid from functioning as a solvent results in a greater condensation of electrolytes in the remainder than would be evident if it were calculated as a uniform concentration in the entire volume. Sunderman and Austin,[42] also Rackemann, Longcope and Peters [43] have shown clinically that febrile disease is accompanied by retention of water, a phenomenon which suggests some alteration of the structures and tissues.

It seems reasonable to believe that when infection is present dehydration, alkalinization and remodeling of globulin proceed as long as it persists or as long as the forms from which it can be derived are in existence. Cannon's [13] insistence on a plentiful supply of protein raw material to feed the chemical "templates" of the reticuloendothelial system applies with equal urgency to the blood stream and the antibodies which originate there. Exhaustion of the proper native proteins results

36. Gortner, R. A.: The Role of Water in Protoplasm, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1932, vol. 1, pp. 21-50; Water in Its Biochemical Relationships, ibid., 1934, vol. 3, pp. 1-19.

37. Jochims, J.: Viscosimetrische Untersuchungen über die Wasserbindung der Plasmakolloide; die Wasserbindung der Eiweisskörper in normalen Blutplasma, Arch. f. d. ges. Physiol. **230**:255-262, 1932.

38. Sunderman, F. W.: The Osmotic Behavior of Water of Blood Serum, J. Biol. Chem. **96**:271-283 (April) 1932.

39. Greenberg, D. M., and Greenberg, M. M.: Ultrafiltration: II. "Bound" Water (Hydration) of Biological Colloids, J. Gen. Physiol. **16**:559-569 (March) 1933.

40. Robinson, W., and Parsons, E.: Hemorrhage and "Shock" in Traumatized Limbs, Arch. Path. **12**:869-888 (Dec.) 1931.

41. Hayasida, A.: The "Non-Solvent Space" of the Serum and the Chlorine Bound by the Serum Protein, J. Biochem. **18**:107-124 (July) 1933.

42. Sunderman, F. W., and Austin, J. H.: Studies of Serum Electrolytes: VI. Water Metabolism in Pneumonia, Am. J. M. Sc. **179**:167-176 (Feb.) 1930.

43. Rackemann, F. M.; Longcope, W. T., and Peters, J. P.: The Excretion of Chlorides and Water and the Renal Function in Serum Disease, Tr. A. Am. Physicians **31**:215-224, 1916.

in a collapse of resistance, which may be averted by blood transfusion or by injection of the proper grade of antiserum. The sulfonamide compounds have of recent years proved a powerful complement to natural immunity. Either without the other may fail, but both together have a remarkable curative record.

The globulin molecule is, in general, much bulkier than the albumin molecule and has a lower colloidal osmotic pressure and a lower solubility. It has been shown that globulin has a molecular weight roughly twice or some other multiple of that possessed by albumin, and it seems not impossible that the increase of globulin represents a joining or polymerization process of the albumin molecules. Schmidt [44] and Astbury, Dickinson and Bailey [45] discuss molecular weights and polymerization of proteins. The writings of Cohn and his associates [46] carry the same thought. They stated: "Actually most globulins have molecular weights of from 140,000 to 170,000, being about twice as large as the albumins, whose molecular weight is in the neighborhood of 73,000. A small proportion of the globulin has the still higher molecular weight of about 900,000, or about twelve times as large as the albumin, and globulin of even larger molecular weight has been observed."

The increase in the nonprotein nitrogen content of the blood in vivo seems to be directly caused by dehydration, which prevents urinary excretion without delaying the progressive accumulation of metabolic nitrogen. This includes, of course, a concentration of the blood as described by Barbour and Gilman,[47] since halving of the volume gives double the concentration of nonprotein nitrogen. In vitro, plasma which has been dried in a vacuum and redissolved in distilled water to the original volume shows an unchanged nitrogen concentration. If it is restored to half its original volume the concentration of nitrogen is doubled. At times of increased concentration there may also be an increment derived from the cells, as described by Bellis and Scott.[48]

The foregoing explanation is of course highly speculative and at present impossible to prove. However, it represents an attempt to group together in their proper relationship certain phenomena which arise as a result of infection and are presumably an integrated and orderly process, not isolated events having no bearing on one another.

The suggestion that the more complex proteins are derived from the simpler ones may reopen a controversy which has existed since the early days of the century, when Moll [50] attempted to convert albumin into globulin by treatment with gentle heat and alkalis and believed that he had succeeded. His results and interpretation have been largely rejected. Other attempts to form globulin have been made at intervals. A more recent one is that of Fischer,[49] who treated albumin with heparin

44. Schmidt, C. L. A.: Chemistry of the Amino-Acids and Proteins, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1932, vol. 1, pp. 151-166; The Chemistry of the Amino Acids and Proteins, ibid., 1933, vol. 2, pp. 71-91.

45. Astbury, W. F.; Dickinson, L., and Bailey, K.: The X-Ray Interpretation of Denaturation and the Structure of the Seed Globulins, Biochem. J. **29**:2351-2360, 1935.

46. Cohn, E. J., and others: Properties and Functions of the Purified Proteins of Animal and Human Plasmas, in Mudd, S., and Thalhimer, W.: Blood Substitutes and Blood Transfusion, Springfield, Ill., Charles C Thomas, Publisher, 1942, pp. 173-180.

47. Barbour, H. G., and Gilman, A.: Heat Regulation and Water Exchange: XVII. The Relation of Serum Osmotic Pressure to the Onset of Fever, J. Pharmacol. & Exper. Therap. **50**:277-285 (March) 1934.

48. Bellis, C. J., and Scott, F. H.: The Alteration of Protein Distribution, in Vitro, Between Corpuscles and Plasma Caused by Isosmotic and Hyperosmotic Solutions, J. Biol. Chem. **111**:17-42 (Sept.) 1935.

49. Fischer, A.: Transformation de la sérumalbumine en sérumglobuline, Compt. rend. Soc. de biol. **108**:882-883 (Dec. 4) 1931.

(antiprothrombin) and concluded that the transformation occurred. Hooker and Boyd [50] disagreed, and at this writing it may be said that the burden of proof rests on those who believe the conversion possible. In his electrophoretic studies Scudder [51] observed that during the preparation of dried transfusion plasma an increase of gamma globulin, the fraction which carries immunity, appeared and that the increase was still present when the plasma was redissolved. The gamma globulin originates from one or more of the native proteins, perhaps the albumin, and possibly through the agency of polymerization, as has previously been suggested. This is an added reason for the use of whole plasma in the preparation of artificial antibodies. The use of purified globulin requires a previous chemical separation of this protein and also eliminates the other forms which are brought into the gamma globulin picture by dehydration and are then available to increase the yield of finished antibodies.

Block, Darrow and Cary [52] concluded that the separation of blood proteins by physicochemical means is an unnatural one and that the globulins and albumins so obtained are artificial products of the reagents used in their preparation. They discovered, through quantitative studies of the constituent amino acids of the total serum protein, an unchanging ratio of arginine to lysine, both in blood from patients with nephrosis with an albumin-globulin ratio of less than 1 and in normal blood with a far higher ratio. In isolated and supposedly pure proteins this is not so, and albumin always gives a larger yield of lysine than does globulin. These observations are evidence that the change is in the state of molecular aggregation rather than intramolecular and are not incompatible with the hypothesis that a polymerization process due to changes in hydration and alkalinity is a cause of protein shift from albumin to globulin which is readily remodeled into antibody protein. The argument over conversion of albumin into globulin is thus reduced to one of no particular immunologic moment. This is perhaps the preferable viewpoint from which to speculate on the exact nature of the changes. Suffice it to say that under the stimulus of dehydration certain of the proteins undergo an alteration of solubility which seems to place them in other groups.

This theory also permits a more detailed explanation of certain nonspecific phases of immunity than has previously been possible. For instance, the intramuscular injection of milk or the intravenous injection of typhoid vaccine is used to cause a reaction which frequently benefits certain types of arthritis. In the past the improvement has usually been attributed to the accompanying leukocytosis and perhaps the increased heat during the period of fever. Now it can be recognized that the changes due to fever include swelling of the protein molecules, reduction of the amount of the free water and an ensuing masked alkalosis. At this juncture much of the gamma globulin is in a plastic or "uncoiled" state, and while some molecules interact with the typhoid or milk antigen others come into contact with the arthritic antigen, which lacks the potency to initiate its own reaction, and are molded into a suitable form to neutralize it.

Immunity has up to the present been described as a systemic process confined to the blood stream. It is logical, however, to believe that it may develop wherever proteins akin to those of the blood are found. In various regional and local infections the signs point to the local development of immunity as a method of anti-

50. Hooker, S. B., and Boyd, W. D.: Alleged Transformation of Serum Albumin into Serum Globulin, J. Biol. Chem. **100**:187-194 (March) 1933.

51. Scudder, J.: Studies in Blood Preservation: The Stability of Plasma Proteins, Ann. Surg. **112**:502-519 (Oct.) 1940.

52. Block, R. J.; Darrow, D. C., and Cary, M. K.: Basic Amino Acids of Serum Proteins. J. Biol. Chem. **104**:347-350 (Feb.) 1934.

bacterial defense. A furuncle, for instance, usually shows in the earlier stages, a small area of redness and pain where the infecting organisms are located. Surrounding this is an area of edema many times larger, which subsides when the infection has been checked and its toxic products neutralized. Drainage and repair of necrotic areas are later developments. The actual furuncular cavity may persist long after immunity is established and the increased water content of the surrounding proteins has vanished. As in the systemic version of the process, leukocytes attracted by the nitrogenous fragments migrate to the center of the disturbance to engulf the offending organisms and form pus. The intercellular lymph closely resembles blood plasma in its chemical characteristics and undoubtedly participates in local immune reactions.

These studies suggest that all preserved blood plasma which has been through a drying process has been subjected to some measure of denaturation and to immunization of an abortive and incomplete type. Scudder [53] has shown by a study of electrophoretic patterns that in plasma dried from a frozen state these changes are minimal, while in liquid or heated plasma they are much greater. If it were considered desirable to prevent the changes and have only the unaltered native proteins, it could perhaps be done by careful control of the p_H range so that it never rose above 7.45 or 7.5.

SUMMARY AND CONCLUSIONS

Recent discoveries indicate that the production of antibodies under laboratory conditions is within the bounds of possibility. Dehydration has been shown to cause conditions favorable to the necessary changes in the proteins of the plasma. The effect of dehydration and the mechanism by which antibodies are produced in the living organism are discussed.

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THERAPY WITH SULFONAMIDE COMPOUNDS FOR PATIENTS WITH DAMAGE TO THE LIVER

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The presence of damage to the liver is one of the few conditions which are still considered to contraindicate the use of sulfonamide compounds or, at least, to require caution in their administration. Many clinical reports, however, include cases in which these drugs have been successfully used for the treatment of infections in the presence of jaundice of varying intensity and for patients with extensive damage to the liver. Adequate studies of the effects of this form of therapy on the hepatic function in such cases are few. In this paper there is reported a series of 37 patients who presented evidence of acute or chronic damage to the liver and who, for various reasons, received either sulfathiazole or sulfadiazine in full therapeutic doses. In each of their cases some studies were made in an attempt to determine the effect of the sulfonamide therapy on hepatic function.

LITERATURE

The liver plays an important role in the metabolism of many organic compounds, including sulfanilamide, its derivatives and some related compounds, notably para-aminobenzoic acid.[1] Indeed, the synthesis of hippuric acid from benzoic acid is a useful test of hepatic function.[1d] The acetylation of sulfanilamide and probably of most of its therapeutically active derivatives takes place chiefly in the liver in some experimental animals, such as the cat,[1g] while in others, notably the rabbit, it is probably confined to that organ.[1f] Acetylation in the rabbit liver has also been shown to take place in vitro.[2] Scudi and his co-workers [3] demonstrated a definite

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2. Klein and Harris.[1b] Harris and Klein.[1c] Van Winkle and Cutting.[1g]

3. (*a*) Scudi, J. V.; Ratish, H. D., and Bullowa, J. G. M.: Increased Glycuronate Excretion Following Administration of Sulfapyridine, Science **89**:516 (June 2) 1939. (*b*) Scudi, J. V., and Robinson, H. J.: Urinary Excretion of Sulfapyridine in the Rat: A Relationship of the Liver to Urolithiasis, Am. J. M. Sc. **201**:711 (May) 1941.

increase in excretion of glucuronic acid during administration of sulfapyridine and concluded that a large part of the "free" drug [4] may really be present in the urine in the form of the highly soluble glucuronate. Sulfanilamide failed to stimulate the output of glucuronic acid, while sulfathiazole did so to a moderate extent. In rats with the liver damaged by phosphorus, the increase in output of glucuronic acid did not occur when sulfapyridine was given, and there was a marked increase in urolithiasis.

There is now considerable evidence that the sulfonamide compounds may produce appreciable damage to the liver in experimental animals and also in man. The frequency and extent of this injury varies with the different derivatives. The available information concerning each of the commonly used sulfonamide compounds will therefore be considered separately.

Sulfanilamide is generally considered to be more injurious to the liver in human therapy than are the other widely used derivatives, but this has not been true in all studies on experimental animals. In rats after prolonged administration of sulfanilamide, Davis, Harris and Schmeisser [5] demonstrated diffuse degeneration of the hepatic parenchyma with focal necrosis and regeneration of cells as evidenced by mitosis. Krems, Martin and Dille [6] also observed increased consumption of oxygen in vitro by the livers of rats which had been subjected to repeated administration of sulfanilamide.

On the other hand, Molitor and Robinson [7] found no evidence of damage to the liver in dogs after prolonged administration of sulfanilamide in large doses. In the livers of rats similarly treated histologic studies revealed nothing significant except some degenerative changes. Greisheimer and her co-workers [8] could not demonstrate any appreciable change in blood sugar or in formation or storage of glycogen after the administration of sulfanilamide in single or repeated doses. Furthermore, there is evidence that the frequency and degree of damage to the liver resulting from carbon tetrachloride poisoning are actually less when sulfanilamide is given at the same time.[9] This protective action of sulfanilamide is not inhibited by paraaminobenzoic acid.[9a] When sulfanilamide is given after the damage from carbon tetrachloride has occurred, it does not interfere with healing.[9a] In animals with obstructive jaundice produced by ligation of the common bile duct no additional damage due to administration of sulfanilamide was discerned. This drug also seems to protect rats from the damage to the liver caused by alcohol.[9c] These findings

4. Marshall, E. K., Jr., and Litchfield, J. T., Jr.: Determination of Sulfanilamide, Science **88**:85 (July 22) 1938.

5. Davis, H. A.; Harris, L. C., Jr., and Schmeisser, H. C.: Tissue Changes Following Prolonged Administration of Sulfanilamide in Rats, Arch. Path. **25**:750 (May) 1938.

6. Krems, A. D.; Martin, A. W., and Dille, J. M.: Experimental Study of Tolerance to Sulfanilamide in the Albino Rat, J. Pharmacol. & Exper. Therap. **71**:215 (March) 1941.

7. Molitor, H., and Robinson, H.: Some Pharmacological and Toxicological Properties of Sulfanilamide and Benzylsulfanilamide, J. Pharmacol. & Exper. Therap. **65**:405 (April) 1939.

8. Greisheimer, E. M.; Hafkesbring, R., and Magalhaes, H.: Blood Sugar and Liver Glycogen: I. After Single Doses of Sulfanilamide, Sodium Sulfapyridine, and Sodium Sulfathiazole, M. Times, New York **69**:170 (April) 1941. Hafkesbring, R.; Greisheimer, E. M., and Wertenberger, G. E.: Blood Sugar and Liver Glycogen: II. Recovery After Single and Repeated Doses of Sulfonamide Drugs, ibid. **69**:467 (Nov.) 1941.

9. (*a*) Forbes, J. C.; Leach, B. E., and Williams, G. Z.: Protective Action of Sulfanilamide Against Liver Cirrhosis from Chronic Poisoning with Carbon Tetrachloride, Proc. Soc. Exper. Biol. & Med. **51**:47 (Oct.) 1942. (*b*) Leach, B. C., and Forbes, J. C.: Sulfonamide Drugs as Protective Agents Against Carbon Tetrachloride Poisoning, ibid. **48**:361 (Oct.) 1941. (*c*) Machella, T. E., and Higgins, G. M.: The Effect of Sulfanilamide on the Experimentally Damaged Liver, Am. J. M. Sc. **204**:194 (Aug.) 1942.

do not necessarily mean that sulfanilamide itself is innocuous to the liver. They suggest, rather, that it may interfere in some way with the action of other toxic agents and reduce the damage done by them.

Since the early clinical reports of Hageman and Blake [10] and Harvey and Janeway,[11] evidence of damage to the liver resulting from administration of sulfanilamide has been presented by a number of observers.[12] Long [12k] found hepatitis with jaundice and impairment of hepatic function in the absence of anemia in 0.6 per cent of patients treated with sulfanilamide. He stated that the prognosis in such cases is good if use of the drug is stopped and fluids are forced. Damage to the liver may appear after a few grams of sulfanilamide has been given, or it may occur only after an extended period of medication. In the 2 cases reported by Spring and Bernstein [12q] there was definite clinical and laboratory evidence of hepatitis after the ingestion of 4.6 Gm. in the one and of 7 Gm. in the other. In other cases damage developed only after prolonged or repeated administration.[13] All grades of damage have been observed, including several instances of acute yellow atrophy, of which

10. Hageman, P. O., and Blake, F. G.: A Specific Febrile Reaction to Sulfanilamide: Drug Fever, J. A. M. A. **109**:642 (Aug. 28) 1937.

11. Harvey, A. M., and Janeway, C. A.: The Development of Acute Hemolytic Anemia During the Administration of Sulfanilamide (Para-Aminobenzene Sulfonamide), J. A. M. A. **109**:12 (July 3) 1937.

12. (*a*) Bannick, E. G.; Brown, A. D., and Foster, F. P.: Therapeutic Effectiveness and Toxicity of Sulfanilamide and Several Related Compounds: Further Clinical Observations, J. A. M. A. **111**:770 (Aug. 27) 1938. (*b*) Berger, S. S., and Applebaum, H. S.: Toxic Hepatitis Due to Sulfanilamide: Report of a Fatal Case with Histopathologic Findings in the Liver, J. Lab. & Clin. Med. **26**:785 (Feb.) 1941. (*c*) Cantarow, A., and Wirts, C. W.: Hyperbilirubinemia Following Administration of Sulfonamides, ibid. **28**:71 (Oct.) 1942. (*d*) Cline, E. W.: Acute Yellow Atrophy of the Liver Following Sulfanilamide Medication, J. A. M. A. **111**:2384 (Dec. 24) 1938. (*e*) De Bonis, G.: Sull'azione epatotossica dei preparati sulfamidici, Athena **9**:248 (Aug.) 1940; abstracted, J. A. M. A. **115**:1928 (Nov. 30) 1940. (*f*) Fitzgibbon, P., and Silver, B.: Toxic Necrosis of the Liver Following the Use of Sulfanilamide, California & West. Med. **50**:123 (Feb.) 1939. (*g*) Garvin, C. F.: Toxic Hepatitis Due to Sulfanilamide, J. A. M. A. **111**:2283 (Dec. 17) 1938. (*h*) Gertlér, W.: Leberparenchymschädigung nach Verabreichung von Prontosil bei chronisch rezidivierendem Erysipel, Dermat. Wchnschr. **106**:725 (June 25) 1939. (*i*) Greene, C. H., and Hotz, R.: Liver and Biliary Tract: A Review for 1938, Arch. Int. Med. **63**:778 (April) 1939. (*j*) Kapnick, I.; Stewart, J. D., and Lyons, C.: Plasma Prothrombin and Liver Function During Sulfonamide Therapy, New England J. Med. **227**:944 (Dec. 17) 1942. (*k*) Long, P. H.; Haviland, J. W.; Edwards, L. B., and Bliss, E. A.: The Toxic Manifestations of Sulfanilamide and Its Derivatives with Reference to Their Importance in the Course of Therapy, J. A. M. A. **115**:364 (Aug. 3) 1940. (*l*) Ottenberg, R.: Acute Yellow Atrophy of the Liver Following Sulfanilamide Therapy and Avertin Necrosis, J. Mt. Sinai Hosp. **6**:249 (Jan.-Feb.) 1940. (*m*) Price, A. E., and Myers, G. B.: Treatment of Pneumococcic Pneumonia with Sulfanilamide, J. A. M. A. **112**:1021 (March 18) 1939. (*n*) Russell, H. K.: Acute Toxic Necrosis of the Liver Following the Use of Sulfanilamide, Ann. Int. Med. **14**:168 (July) 1940. (*o*) Saphirstein, H.: Hepatitis and Toxic Erythema with Desquamation Due to Sulfanilamide, Urol. & Cutan. Rev. **42**:101 (Feb.) 1938. (*p*) Spink, W. W.: Sulfanilamide and Related Compounds in General Practice, ed. 2, Chicago, Year Book Publishers, Inc., 1942, p. 294. (*q*) Spring, M., and Bernstein, I.: The Coexistence of Toxic Hepatitis, Acute Hemolytic Anemia and Renal Damage Following Sulfanilamide Therapy: Report of Two Cases, Ann. Int. Med. **14**:153 (July) 1940. (*r*) Tragerman, L. J., and Goto, J. M.: Fatal Reactions to Administration of Sulfonamide Drugs, J. Lab. & Clin. Med. **25**:1163 (Aug.) 1940. (*s*) Watson, C. J.: The Bile Pigments, New England J. Med. **227**:665 (Oct. 29); 705 (Nov. 5) 1942. (*t*) Watson, C. J., and Spink, W. W.: Effect of Sulfanilamide and Sulfapyridine on Hemoglobin Metabolism and Hepatic Function, Arch. Int. Med. **65**:825 (April) 1940.

13. Bannick, Brown and Foster.[12a] Fitzgibbon and Silver.[12f] Garvin.[12g] Gertlér.[12h] Ottenberg.[12l] Saphirstein.[12o]

some ended fatally.[14] Toxic hepatic necrosis has also followed the use of the original prontosil (hydrochloride of 4′-sulfonamido-2′-4′-diaminoazobenzene) and azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate), either alone or in conjunction with sulfanilamide.[15] Garvin [12g] observed an acute exfoliative dermatitis in 3 of his 5 cases of hepatitis resulting from sulfanilamide therapy, and Saphirstein [12o] reported a similar case.

The most thorough studies of hepatic function in patients treated with sulfanilamide were carried out by Watson and Spink.[12t] They demonstrated urobilinogenuria, elevated serum bilirubin or frank jaundice in an appreciable number of cases. The jaundice was of the regurgitation type and was frequently associated with a direct van den Bergh reaction. It was encountered chiefly when large therapeutic doses were employed, while after small doses, such as those frequently used in treating infections of the urinary tract, hepatic dysfunction was less apt to occur. Similar findings were reported recently by Cantarow and Wirts.[12c] Kapnick, Stewart and Lyons [12j] demonstrated a fall in plasma prothrombin as an early sign of hepatic dysfunction in the course of sulfonamide therapy. De Bonis [12e] noted jaundice, enlargement of the liver and urobilinuria during the first week of sulfanilamide therapy in 2 cases. Using tests for galactose tolerance and tests with aminoacetic acid, he found evidence of hepatic disturbance in 5 of 11 normal subjects after a dose of 0.003 Gm. per kilogram of body weight. Studies of hepatic function in cases of hemolytic anemia developing during sulfanilamide therapy have also revealed mild impairment in some instances.[16]

Schmidt,[17] on the other hand, found no reduction in hepatic function, as judged by tests of galactose tolerance, during sulfanilamide therapy. He was studying patients with gonococcic infections who were being treated with rather small doses. He found that such patients often had reduced hepatic function before treatment and that sulfanilamide always had a favorable influence. Sulfanilamide has also been used in isolated cases of obstructive jaundice and biliary cirrhosis associated with obstruction of the common bile duct [18] as well as in cases of suppurative pylephlebitis and hepatic abscesses without evidence of aggravation of the antecedent damage to the liver.[19]

Bannick, Brown and Foster [12a] observed 2 cases of jaundice following sulfanilamide therapy in which death occurred and in which there may have been preexisting hepatic damage. They felt that sulfanilamide may cause such preexisting damage to progress to a stage from which regeneration is impossible. Watson [20] also has stated that in his experience severe and progressive hepatic injury is seen only when there is reason to believe that the liver was damaged before the admin-

14. Berger and Applebaum.[12b] Cline.[12d] Greene and Hotz.[12i] Ottenberg.[12l] Tragerman and Goto.[12r]

15. Gertlér.[12h] Russell.[12n]

16. One patient studied by Ham and Deutsch (personal communication to the authors) had a severe hemolytic anemia from sulfanilamide, accompanied by severe damage to the liver with increased urobilinogenuria and diminished synthesis of hippuric acid. The signs of hepatic insufficiency cleared promptly when administration of the drug was stopped. See also Harvey and Janeway [11] and Watson and Spink.[12t]

17. Schmidt, W.: Leberfunktionsprüfungen bei Therapie mit Sulfamidkörpern, Klin. Wchnschr. **18**:953 (July 15) 1939; abstracted, J. A. M. A. **113**:1607 (Oct. 21) 1939.

18. Cleveland, W. H.: Sulfanilamide Therapy in Presence of Severe Injury to the Liver and Jaundice, Proc. Staff Meet., Mayo Clin. **14**:680 (Oct. 25) 1939.

19. Ottenberg, R., and Berck, M.: Sulfanilamide Therapy for Suppurative Pylephlebitis and Liver Abscesses, J. A. M. A. **111**:1374 (Oct. 8) 1938.

20. Watson, C. J.: The Effect of Sulfanilamide upon the Liver, Surgery **5**:616 (April) 1939; footnote 12 *s*.

istration of the sulfanilamide, for example, in the presence of severe infection or toxemia or when the drug was given to a patient who also received arsphenamine treatment for syphilis. Among Kapnick's cases [12j] the greatest reduction in plasma prothrombin occurred during treatment with sulfanilamide in a patient with known biliary cirrhosis who previously had a prolonged prothrombin time and had received vitamin K.

The implantation of sulfonamide compounds into the peritoneal cavity after abdominal operations is a procedure carried out with varying regularity by many surgeons, particularly when infection is present or anticipated. Because of its greater solubility, sulfanilamide is usually chosen for this purpose, and in a number of instances hepatic damage has resulted from its use in this manner.[21] In most of the cases oral doses were used in addition. While a considerable depression of hepatic function is thought by some surgeons to occur after any abdominal operation, regardless of the type of anesthesia used,[22] the damage to the liver in most of the patients treated with sulfonamide compounds could usually be attributed definitely to the drug and improved when treatment with it was discontinued. In some instances large doses (up to 20 Gm.[21a]) had been implanted. Possibly the high concentration attained, together with the sepsis, was responsible for the injury to the liver in certain cases. Blood from the portal vein may, for a short period after abdominal implantation of sulfanilamide, have a concentration of the drug 40 per cent higher than that in the peripheral venous blood,[21b] but the levels are usually the same after about four hours.[23] Levels of 400 to 800 mg. per hundred cubic centimeters of peritoneal fluid have been noted as long as forty hours after a single implantation of sulfanilamide.[24] Some surgeons have observed no serious local or general effects from the intraperitoneal use of this drug in many cases.[25]

Sulfapyridine, like sulfanilamide, has been found to produce damage to the liver both in experimental animals and in patients. In monkeys, sulfapyridine causes its greatest damage to the kidneys, but a "serous" hepatitis has been described.[26] Some of the hepatic cells appear vacuolated and contain large droplets, and pigment is seen in the Kupffer cells, but actual necrosis is not observed.[27] In rats, single or multiple doses of sodium sulfapyridine result in an elevation in blood sugar and an alteration in the storage and formation of glycogen which increases with the size of the dose.[6] No microscopic damage ascribable to sulfapyridine has been noted in experiments producing chronic toxicity in rats,[28] but foci of necrosis were

21. (*a*) Dees, J. G.: A Valuable Adjunct in Perforated Appendices, Mississippi Doctor **18**:215 (Sept.) 1940. (*b*) Jackson, H. C., and Coller, F. A.: The Use of Sulfanilamide in the Peritoneum: Experimental and Clinical Observations, J. A. M. A. **118**:194 (Jan. 17) 1942. (*c*) Ravdin, I. S.; Rhoads, J. E., and Lockwood, J. S.: The Use of Sulfanilamide in the Treatment of Peritonitis Associated with Appendicitis, Ann. Surg. **111**:53 (Jan.) 1940.

22. Boyce, F. F.: The Role of the Liver in Surgery, South. Surgeon **10**:56 (Jan.) 1941.

23. Pearce, A. E.: Intraperitoneal Administration of Sulfanilamide, Correspondence, J. A. M. A. **120**:982 (Nov. 21) 1942.

24. Mueller, R. S., and Thompson, J. E.: The Local Use of Sulfanilamide in the Treatment of Peritoneal Infections, J. A. M. A. **118**:189 (Jan. 17) 1942,

25. Thompson, J. E.; Brabson, J. A., and Walker, J. M.: The Intra-Abdominal Application of Sulfanilamide in Acute Appendicitis, Surg., Gynec. & Obst. **72**:722 (April) 1941. Mueller and Thompson.[24]

26. Antopol, W., and Robinson, H.: Pathologic and Histologic Changes Following Administration of Sulfapyridine, with a Short Note on Sodium Sulfapyridine, Arch. Path. **29**:67 (Jan.) 1940.

27. Feinstone, W. H., and others: The Toxicity, Absorption and Chemotherapeutic Activity of 2-Sufanilamidopyrimidine (Sulfadiazine), Bull. Johns Hopkins Hosp. **67**:427 (Dec.) 1940.

28. Walker, H. A., and van Dyke, H. B.: Observations on the Toxicology of Sulfathiazole and Some Related Compounds, J. Pharmacol. & Exper. Therap. **71**:138 (Feb.) 1940.

noted in the livers of mice fed large doses of this drug.[29] Like sulfanilamide, sulfapyridine seems to protect the livers of rats from damage by carbon tetrachloride.[9b] The failure of rats whose livers have been injured by phosphorus to show an increased glucuronate output while being given sulfapyridine and the resulting increase in urolithiasis [3b] have already been mentioned.

In human beings, fatty changes in the liver with fine globules uniformly distributed in the hepatic cells were noted by Brown, Thornton and Wilson [30] in all patients who died of pneumonia after sulfapyridine therapy. This was interpreted as probably due to the toxicity resulting from the disease. In 1 of their patients jaundice and enlargement of the liver developed, but eventually receded. These workers later reported the findings of sulfapyridine in the liver from ten to forty days after the last dose,[31] but they would draw no conclusions as to whether sulfapyridine causes hepatitis. Long and Wood [32] noted 1 patient with sulfapyridine-treated pneumonia who had hepatitis associated with jaundice in the absence of acute hemolytic anemia. In the case reported by Cutts and Bowman [33] jaundice and aching in the right upper quadrant of the abdomen accompanied the hematuria and encephalopathy which followed the intravenous administration of 20 Gm. of sodium sulfapyridine over a ten hour period. All the symptoms subsided fairly promptly. Two cases of hepatitis from sulfapyridine in children were reported by Leopold and Sobel.[34] Spink [12p] and Watson and Spink [12t] encountered mild hepatitis in occasional sulfapyridine-treated patients, but they found much less disturbance of hepatic function than among the ones treated with sulfanilamide. Others have also reported evidence of hepatic dysfunction, such as hyperbilirubinemia, urobilinogenuria [35] and decreased plasma prothrombin,[12j] in sulfapyridine-treated patients with pneumonia and other infections. It should be mentioned, however, that some patients with severe hepatitis have been successfully treated for pneumonia with sulfapyridine and have not shown any evidence of increase in the damage to the liver.[36]

Sulfathiazole has proved less toxic to the liver than either sulfapyridine or sulfanilamide, both for laboratory animals and for human beings. In dogs given large doses renal function is depressed but hepatic function is not affected.[37] In

29. Rake, G.; van Dyke, H. B., and Corwin, W. C.: Pathologic Changes Following Prolonged Administration of Sulfathiazole and Sulfapyridine, Am. J. M. Sc. **200**:353 (Sept.) 1940.

30. Brown, W. H.; Thornton, W. B., and Wilson, J. S.: Observations on the Absorption, Distribution and Excretion of Sulfapyridine, J. Clin. Investigation **18**:803 (Nov.) 1939.

31. Brown, W. H.; Thornton, W. B., and Wilson, J. S.: An Evaluation of the Clinical Toxicity of Sulfanilamide and Sulfapyridine, J. A. M. A. **114**:1605 (April 27) 1940.

32. Long, P. H., and Wood, W. B., Jr.: Observations upon the Experimental and Clinical Use of Sulfapyridine: II. The Treatment of Pneumococcic Pneumonia with Sulfapyridine, Ann. Int. Med. **13**:487 (Sept.) 1939.

33. Cutts, F. B., and Bowman, R. O.: Toxic Effects in Man of Overdosage with Sodium Sulfapyridine: Report of a Case, New England J. Med. **225**:448 (Sept. 18) 1941.

34. Leopold, J. S., and Sobel, I. P.: Sulfapyridine Therapy in Pneumonias of Infancy and Childhood, Arch. Pediat. **56**:581 (Sept.) 1939.

35. Erf, L. A., and McLeod, C. M.: Increased Urobilinogen Excretion and Acute Hemolytic Anemia in Patients Treated with Sulfapyridine, J. Clin. Investigation **19**:451 (May) 1940. Cantarow and Wirts.[12e]

36. Finland, M.; Lowell, F. C., and Strauss, E.: Treatment of Pneumococcic Pneumonia with Sulfapyridine, Sulfathiazole and Serum, Ann. Int. Med. **14**:1184 (Jan.) 1941. Brown, Thornton and Wilson.[31]

37. Climenko, D. R.; McChesney, E. W., and Messer, F.: Continued Administration of Sulfathiazole on Renal and Hepatic Function in the Dog, Proc. Soc. Exper. Biol. & Med. **46**: 124 (Jan.) 1941.

rats, sodium sulfathiazole produces a definite increase in blood sugar but does not affect hepatic glycogen unless highly toxic doses are used.[8] Microscopic changes are seen in the livers of rats which receive large doses.[29] No such lesions have been produced during the usual experiments for producing chronic toxicity in rats,[28] but they have been seen during similar studies on mice.[38]

Isolated instances of hepatitis have been noted in patients receiving sulfathiazole in the usual therapeutic doses.[39] In 1 patient hepatitis with severe jaundice and enlarged liver but without anemia accompanied the development of agranulocytosis. This patient was treated for pneumonia and empyema by prolonged administration [40] of sulfathiazole. Rammelkamp [41] observed a patient in whom, after a course of sulfathiazole therapy, fever, jaundice, and enlargement of the liver developed. The complication cleared slowly when use of the drug was discontinued. One month later the administration of a single dose of 0.5 Gm. of the same drug was followed rapidly by a recurrence of the same symptoms. Studies of hepatic function have shown some impairment during administration of sulfathiazole similar to that found in patients treated with sulfapyridine.[42] Hepatic dysfunction, with bile and urobilinogen in the urine, decreased output of hippuric acid and retention of bromsulphalein, was noted in 1 case of hemolytic anemia following sulfathiazole therapy.[43] In another case of acute hemolytic anemia from sulfathiazole, no hepatic dysfunction was demonstrated,[44] while in a third the liver was enlarged and tender.[45] In a recent case [46] extensive focal necrosis of the liver, kidneys, spleen and adrenals was ascribed to the toxicity of sulfathiazole.

Sulfamethylthiazole when given as the sodium salt to rats produces severe renal damage with nitrogen retention. Associated with this there is also increased glycogen in the liver and definite hepatic injury.[47] No gross or microscopic lesions attributable to this drug were noted during experiments for producing chronic toxicity in rats.[28] There is little information concerning hepatic injury in human therapy, but sulfamethylthiazole drug has not been used extensively.

Sulfadiazine produces no demonstrable damage to the liver in mice, rats or monkeys.[27] Cantarow and Wirts [12c] found hepatic injury in 3 patients treated with sulfadiazine. This was evidenced by bilirubinemia, urobilinogenuria, retention of bromsulphalein and diminished output of hippuric acid. Kapnick, Stewart and Lyons [12j] observed a reduction of plasma prothrombin in 2 patients treated with sulfadiazine, but in 1 of them the prothrombin time returned to normal after five

38. Long, P. H.: Thiazole Derivatives of Sulfanilamide: Sulfathiazole and Sulfamethylthiazole, J. A. M. A. **114**:870 (March 9) 1940.

39. Cantarow and Wirts.[12c] Spink.[12p] Finland, Lowell and Strauss.[36]

40. McCarty, W. C., and Finland, M.: Personal communication to the authors.

41. Rammelkamp, C. H.: Personal communication to the authors.

42. Cantarow and Wirts.[12c] Kapnick, Stewart and Lyons.[12j]

43. Rothstein, I., and Cohn, S.: Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy: Case Report, Ann. Int. Med. **16**:152 (Jan.) 1942.

44. Quick, E. D., and Lord, F. D.: Acute Hemolytic Anemia Following Sulfathiazole Administration: Report of a Case with Recovery, J. A. M. A. **117**:1704 (Nov. 15) 1941.

45. Bunin, J. J., and Israel, M.: Acute Hemolytic Anemia Caused by Sulfathiazole, Ann. Int. Med. **16**:333 (Feb.) 1942.

46. Simon, M. A., and Kaufman, M.: Death Following Sulfathiazole Therapy, Canad. M. A. J. **48**:23 (Jan.) 1943.

47. Lehr, D.; Churg, S., and Antopol, W.: Mechanism of Liver and Kidney Damage Caused by Sodium Sulfamethylthiazole, Proc. Soc. Exper. Biol. & Med. **45**:447 (Oct.) 1940.

days during which the patient continued to receive large doses of this drug. In our own [48] and in Spink's [12p] experience no evidence of damage to the liver has been noted in large numbers of sulfadiazine-treated patients with all types of infections. Some patients with severely impaired hepatic function have been treated with full doses of sulfadiazine for various diseases without ill effects and even with improvement in hepatic function during treatment.[48] Spink has recommended its use in cases of cirrhosis of the liver when a sulfonamide compound is indicated.[12p]

MATERIALS AND METHODS

The patients studied were all admitted to the Boston City Hospital during 1941 and the first half of 1942. Only those patients are included in whom there was clinical and laboratory evidence of damage to the liver and in whom tests of hepatic function were made before and after a course of some sulfonamide compound. In many of these cases repeated tests were made both during the sulfonamide therapy and for some time later. A large number of other similar patients treated with sulfonamide compounds were observed during this period, but they are not included here because of inadequate data.

In 13 of the cases a diagnosis of acute hepatitis was made; in them the damage to the liver was, for the most part, secondary to an acute pyogenic infection, except in 1 case in which a diagnosis of catarrhal jaundice was made. The remaining patients had chronic disease of the liver and included 14 with portal cirrhosis, 5 with biliary cirrhosis, 4 with damage to the liver resulting from chronic congestive cardiac failure and 1 with diffuse carcinomatosis.

To most of the patients the sulfonamide compound was given in the usual therapeutic doses and for a definite pyogenic infection. To a few, however, the drug was given because of a suspected infection, the presence of which was not substantiated. Sulfathiazole and sulfadiazine were each used alone for 14 patients; both were given in succession or on separate occasions to 7, and 2 received sulfapyridine. The average total dose per patient was 44 Gm. Those treated with both sulfathiazole and sulfadiazine received an average total dose of 56 Gm.

Several tests of hepatic function were employed and the icterus index was determined frequently in every case. The hippuric acid test was carried out according to the gravimetric method of Quick.[1d] A fractional bromsulphalein test was performed by injecting 2 mg. of dye per kilogram of body weight and estimating the amount of dye retained after five and fifteen minutes, according to the method described recently by Deutsch.[49] The prothrombin time was measured by Souter and Kark's [50] modification of Quick's [51] method. Tests were made for bile in the urine; and its urobilinogen content was estimated by the dilution method of Wallace and Diamond [52] in most instances. In a few cases daily quantitative determinations of urobilinogen were made by the method of Watson.[53] Several of these tests were usually carried out in each case. The concentrations of sulfonamide compounds in the blood and the urine were determined at frequent intervals by the method of Bratton and Marshall.[54]

The clinical course of the patients was followed closely from day to day. Therapy for the disease of the liver included diets high in carbohydrate and protein and low in fat, brewers'

48. Finland, M.; Strauss, E., and Peterson, O. L.: Sulfadiazine: Therapeutic Evaluation and Toxic Effects in Four Hundred and Forty-Six Patients, J. A. M. A. **110**:2641 (June 14) 1941. Finland, M.; Peterson, O. L., and Goodwin, R. A., Jr.: Sulfadiazine: Further Clinical Studies of Its Efficacy and Toxic Effects in Four Hundred and Sixty Patients, Ann. Int. Med. **17**:920 (Dec.) 1942.

49. Deutsch, E.: A Fractional Bromsulfalein Test to Determine Liver Damage in the Non-Jaundiced Patient, New England J. Med. **225**:171 (July 31) 1941.

50. Souter, A. W., and Kark, R.: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, Am. J. M. Sc. **200**:603 (Nov.) 1940.

51. Quick, A. J.; Stanley-Brown, M., and Bancroft, F. W.: A Study of the Coagulation Defect in Hemophilia and in Jaundice, Am. J. M. Sc. **190**:501 (Oct.) 1935.

52. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, with a Description of a Simple Quantitative Method for Its Estimation, Arch. Int. Med. **35**:698 (June) 1925. This method may give false high readings during therapy with sulfonamide compounds.[49]

53. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**:458 (Sept.) 1936.

54. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, J. Biol. Chem. **128**:537 (May) 1939.

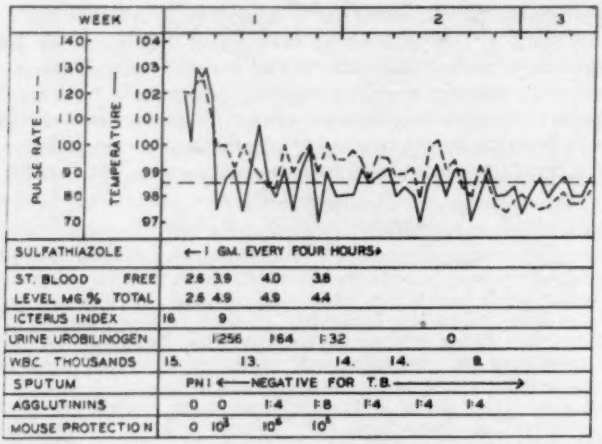

Chart 1.—Clinical chart and relevant laboratory data in case 5. A man of 50 with type I pneumococcus lobar pneumonia involving the middle and the lower lobe of the right lung was admitted to the hospital on the sixth day of illness with mild jaundice, slightly enlarged liver and bile-stained urine. Blood culture showed no growth. The temperature and pulse rate dropped to normal after thirty-six hours of sulfathiazole therapy. The jaundice and the other symptoms of acute hepatitis improved rapidly thereafter.

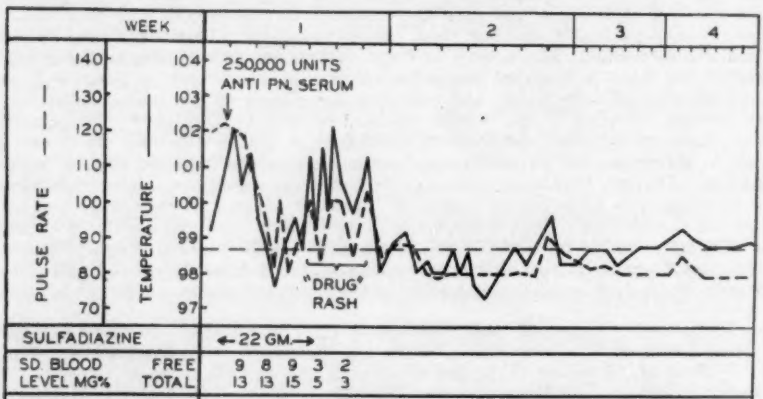

Chart 2.—Chart of case 3. A man of 68 with a history of excessive intake of alcohol and a previous episode of jaundice thirty years ago was admitted to the hospital on the ninth day of a severe lobar pneumonia involving the upper lobe of the right lung. He had moderately intense jaundice of two days' duration. At entry the edge of the liver was felt 8 cm. below the costal margin and was tender. After treatment with sulfadiazine and antipneumococcus serum the fever and toxic symptoms subsided, the jaundice cleared, and the liver edge receded gradually. The nonprotein nitrogen content of the blood was elevated at the time of the patient's admission to the hospital. It increased temporarily and then returned to normal after administration of the drug was stopped (see also table 1). This patient probably had underlying portal cirrhosis.

TABLE 1.—*Patients with Acute Hepatitis (? Toxic or Infectious Jaundice) Who Received Therapy with Sulfonamide Compounds*

Case, Sex and Age	Diagnosis	Results of Tests of Hepatic Function: Before Therapy with Sulfonamide Compounds — I. I.	Bile in Urine	Urine Urobilinogen	H. A.	Prothrombin	After Therapy with Sulfonamide Compounds — I. I.	Bile in Urine	Urine Urobilinogen	H. A.	Prothrombin	B. S. P. 5 Min.	B. S. P. 15 Min.	Estimate of Hepatic Dysfunction	Therapy with Sulfonamide Compounds: Drug	Total Amount, Gm.	Toxicity	Comments
1 M 26	Pneumococcus, type 8 pneumonia	50	0	1:256	—	—	7	0	1:32	3.0	—	50	5	Mild	ST	41	Fever, rash	Rapid recovery
2 F 57	Pneumococcus, type 3 pneumonia	25	+	1:16	—	40	5	0	N	0.6	100	—	—	Severe	ST	33	NPN rise of 12 mg. per 100 cc.	Residual damage to liver at discharge
3 M 68	Pneumococcus, type 14 pneumonia	50	+	1:32	1.3	56	10	0	N	1.0	80	30	5	Severe	SD	22	Fever, rash, NPN rise	Residual damage to liver (? cirrhosis) at discharge (chart 2)
4 F 30	Pneumococcus, type 3 pneumonia	80	0	1:64	3.4	—	10	0	N	2.5	100	—	—	Mild	SD	57	None	Complete recovery
5 M 50	Pneumococcus, type 1 pneumonia	16	+	1:256	—	—	9	0	N	—	—	—	—	Mild	ST	51	None	Complete recovery (chart 1)
6 F 55	Lobar pneumonia; parkinsonism	18	0	1:80	—	—	5	0	1:20	—	—	—	—	Mild	SD	17	None	Rapid recovery
7 F 42	B. coli sepsis; ? liver abscesses; chronic ulcerative colitis	60	+	1:128	0.7	100	6	0	N	3.0	100	—	—	Severe	ST SD	65 28	None	Gradual improvement of infection and hepatitis during chemotherapy
8 M 74	Carcinoma of colon; postoperative sepsis in wound; SA implantation	110	+	15 mg.*	1.8	40	10	0	7 mg.*	2.2	55	30	0	Severe	ST	55	None	Hepatitis and sepsis improved under ST therapy
9 M 77	Pyelonephritis; acute hepatitis	80	++	1:32	1.0	52	10	0	N	3.7	100	5	0	Mild	ST	10	None	Complete recovery; cause of hepatitis unknown
10 F 44	Acute hepatitis (? cause); streptococcic pharyngitis	90	—	1:256	1.5	63	10	0	N	2.7	—	—	—	Mild	SD	53	None	Rapid recovery
11 F 49	? Catarrhal jaundice	75	++	1:256	1.5	100	10	0	N	3.0	—	5	0	Moderate	SD	26	None	Steady improvement on SD
12 F 26	Pylephlebitis, pregnancy, ulcerative colitis, peritonitis	75	++	—	—	—	25	++	—	0	—	—	—	Severe	ST SD	16 46	None	Died: abscesses of liver found at autopsy; putrid empyema
13 M 74	Lobar pneumonia	75	++	—	—	—	10	0	—	—	—	—	—	Mild	SP	22	None	Cleared rapidly

Abbreviations: I. I., icterus index; urine urobilinogen, figures represent dilutions (method of Wallace and Diamond [52]), N, 1:16 or less (normal); H. A., hippuric acid recovered from urine after ingestion of 6 Gm. of sodium benzoate; prothrombin, concentration expressed in per cent of normal (Quick rapid method as modified by Soutter and Kark [54]); B. S. P., bromsulphalein, percentage retained in serum; SA, sulfanilamide; SP, sulfapyridine; ST, sulfathiazole; SD, sulfadiazine; NPN, blood nonprotein nitrogen in mg. per 100 cc.; —, data not available.

* Watson method [53], numbers represent milligrams per day.

yeast or a preparation of autolyzed yeast (vegex) in doses of 6 to 12 Gm. daily, parenterally administered vitamins and crude liver extracts when they seemed indicated and carbohydrate supplements in the form of corn syrup (Karo).

RESULTS

Patients with Acute Hepatitis.—The essential data concerning the 13 patients listed in this category are given in table 1. In 7 of the cases, the hepatitis was secondary to severe lobar pneumonia. In each of these 7 cases jaundice cleared and hepatic function improved with sulfonamide therapy. Chart 1 gives data for a typical case. Two of the 7 patients had evidence of some residual damage to the liver as indicated by diminished excretion of hippuric acid at the time of discharge from the hospital. One of these 2 patients (case 3, chart 2) had a high nonprotein nitrogen level in the blood at entry, and this increased appreciably during sulfadiazine treatment but returned to normal after the drug was stopped. The other patient (case 2) had a slight elevation of the level of nonprotein nitrogen in the blood during sulfathiazole treatment.[55] Both of these patients were clinically well when they left the hospital. The former probably had an underlying portal cirrhosis with acute hepatitis resulting from the pneumonia.

In 3 patients the cause of the acute hepatitis was uncertain. In 1 of them a diagnosis of catarrhal jaundice was made, and there was no evidence of any other infection. The second had a streptococcic pharyngitis and the third had a colon bacillus pyelonephritis. In each of these patients there was rapid recovery with steady improvement in hepatic function, which returned to normal during sulfathiazole or sulfadiazine therapy.

One of the patients (case 7), a woman of 60, had colon bacillus sepsis and probably multiple abscesses of the liver complicating chronic ulcerative colitis. She was treated first with sulfathiazole and then with sulfadiazine and showed gradual improvement both in the infection and in the hepatitis during the treatment. In another patient (case 12), a woman of 26, acute ulcerative colitis developed during the course of pregnancy, and she was admitted to the hospital because of rupture of the bowel, which was followed by peritonitis, generalized sepsis, acute hepatitis, pneumonia and putrid empyema. The jaundice improved during sulfathiazole and sulfadiazine therapy, but the patient died after two weeks. At autopsy multiple abscesses of the liver were found.

Case 8 is of special interest. In this patient, a man of 74, the peritoneal cavity was contaminated with feces in the course of a cecostomy performed to relieve a complete obstruction of the descending colon due to carcinoma. At the time of operation, 10 Gm. of sulfanilamide was sprinkled into the peritoneal cavity and the cecostomy wound. On the following day there was evidence of both peritonitis and sepsis in the wound and the patient became jaundiced. Treatment with sulfathiazole was started, and a total of 55 Gm. was given in nine days. During this time both the infection in the wound and the signs of peritonitis cleared; the icterus index dropped from 110 to 10, and the excretion of hippuric acid increased slightly. Two weeks later the bromsulphalein test showed no retention of the dye in fifteen minutes, but there was still an increased output of urobilinogen in the urine (7 mg. per day by Watson method). An exploratory operation performed after five weeks revealed numerous metastases in the liver and omentum. The patient died four months later with progressive cachexia. This case presents a good example of acute hepatitis resulting from intraperitoneal sepsis and implantation of sulfanilamide, in which the hepatitis resolved when the infection was cured by administration of sulfathiazole.

55. The excretion of hippuric acid is, of course, diminished in the presence of renal damage which is associated with retention of nitrogen.

Patients with Chronic Disease of the Liver.—Twenty-four patients with chronic disease of the liver are included in this study. The damage to the liver was classified as severe in 13 of the cases and moderate in the remainder, except 1 in which it was considered to be mild. The clinical diagnosis was portal cirrhosis (Laennec) in 14 cases, biliary cirrhosis in 5 and chronic passive congeston or cardiac cirrhosis in 4, while in 1 case there was an old cirrhosis of undetermined type with superimposed metastatic carcinoma. The cases of portal cirrhosis occurred chiefly in patients with a history of prolonged and excessive alcoholic intake and faulty nutrition. The biliary cirrhosis was secondary to obstruction, resulting from stenosis of the common bile duct in 2 cases, from cholelithiasis in 2 others and from carcinoma of the gallbladder in 1 case.

Sulfathiazole and sulfadiazine were each used alone in 9 cases; both were used either in succession or at different times in 5, while in 1 sulfapyridine was given. The drugs were used chiefly for the treatment of pneumonia, hemolytic streptococcic infections, such as pharyngitis or erysipelas, and infections of the urinary tract. They were given in full therapeutic doses.

All of the patients also received intensive therapy for their hepatic disease. The exacerbations and remissions which characterize the healing process in cirrhosis of the liver have frequently made very difficult an evaluation of the effects of the sulfonamide therapy. Furthermore, the oliguria so often associated with the severe relapses in the cases of portal cirrhosis would appear greatly to enhance the hazards of this form of treatment.

Some of the relevant data in these cases and the results of the tests of hepatic function carried out before and after the sulfonamide therapy are listed in table 2. So far as hepatic function is concerned, the patients with chronic disease of the liver seemed to tolerate the drugs well. Eleven of the patients showed improvement in hepatic function during sulfonamide therapy concomitant with the clearing up of the infection for which the drugs were given. In 11 other patients there was no apparent change in the status of the liver, although the infection in most of these cases was favorably influenced by the sulfonamide therapy. In 2 patients (cases 19 and 31) there may have been some temporary aggravation of the hepatic dysfunction during the chemotherapy at a time when they were manifesting other toxic reactions from the drugs.

In view of the role of the liver in the acetylation and detoxification of the sulfonamide compounds, it is of interest that the conjugation of these drugs in this group of patients was apparently unaffected. At least the percentage of drug found in the conjugated form (by the method of Bratton and Marshall [54]) both in blood and in urine of these patients was essentially the same as in the general run of patients without disease of the liver.[56]

A brief summary of 3 representative case reports will serve to indicate the variations in the results of the tests of hepatic function observed in some of the present cases:

CASE 25 (chart 3).—A 40 year old white laborer had been a heavy consumer of alcoholic beverages for fifteen years. For a year before he entered the hospital his appetite had been poor. His abdomen had been increasing in size for four or five months, and for the last five or six weeks he had noticed that his skin and scleras were jaundiced. At the time of admission

56. Peterson, O. L.; Strauss, E.; Taylor, F. H. L., and Finland, M.: Absorption, Excretion, and Distribution of Sulfadiazine (2-Sulfanilamido-Pyrimidine), Am. J. M. Sc. **201**:367 (March) 1941. Strauss, E.; Lowell, J. C.; Taylor, F. H. L., and Finland, M.: Observations on the Absorption, Excretion, and Distribution of Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfamethylthiazole, Ann. Int. Med. **14**:1360 (Feb.) 1941.

TABLE 2.—*Relevant Data on Patients Treated with Sulfonamide Compounds Who Had Portal or Biliary Cirrhosis or Chronic Passive Congestion of the Liver (Cardiac Cirrhosis ?)*

Case, Sex and Age	Diagnosis	Results of Tests of Hepatic Function: Before Therapy with Sulfonamide Compounds — I. I.	Bile in Urine	Urine Urobilinogen	H. A.	Prothrombin	B. S. P. 5 Min.	B. S. P. 5 Min.	After Therapy with Sulfonamide Compounds — I. I.	Bile in Urine	Urine Urobilinogen	H. A.	Prothrombin	B. S. P. 5 Min.	B. S. P. 5 Min.	Estimate of Hepatic Dysfunction	Therapy with Sulfonamide Compounds: Drug	Total Amount, Gm.	Toxicity	Comments (Effects of Therapy with Sulfonamide Compounds)
14 M, 27	Pneumonia, Pn 8; portal cirrhosis	20	+	1:32	1.1	45	—	—	10	0	1:8	1.1	80	—	—	Severe	ST	40	Rash, fever	Improved while on ST
15 M, 48	Pneumonia, Pn 14; portal cirrhosis	50	++	1:256	2.6	20	60	40	10	0	1:6	2.2	50	100	15	Severe	ST SD	35 53	Fever (ST)	Pneumonia improved; liver status unchanged
16 F, 46	Pneumonia, Pn 3 + SH; portal cirrhosis	35	+	1:128	2.5	100	—	—	10	0	N	0.5	—	—	—	Severe	ST SD	23 9	Fever (ST)	Infection increased damage to liver; improved on ST
17 M, 57	Bronchopneumonia; portal cirrhosis	<10	0	—	—	65	40	10	<10	0	—	0.7	—	40	20	Moderate	ST	72	NPN rose 20 mg. per 100 cc.	Pneumonia improved; liver status unchanged
18 M, 28	Bronchopneumonia; portal cirrhosis	35 10	++	1:128	3.1	68	70	5	5	0	1:4	—	100	—	—	Moderate	SD	25	Hematuria, renal colic	Liver status unchanged
19 M, 54	Bronchopneumonia; portal cirrhosis	60 20	+	1:128	1.0	60	60	60	65 15	0	—	1.2	70	—	—	Moderate	SD†	26	Hematuria, colic, fever	Jaundice and ascites temporarily increased under SD
20 M, 55	Erysipelas; portal cirrhosis	100	—	1:256	1.6	85	—	—	8	—	1:32	—	80	—	—	Severe	SD	24	None	Good clinical response
21 M, 35	SH pharyngitis; portal cirrhosis	75	+	1:32	—	—	—	—	15	0	N	—	—	—	—	Moderate	SP	13	Hematuria, anuria 24 hrs.	Rapid improvement with return of normal output of urine
22 F, 46	Pyelitis; B. coli; portal cirrhosis	25	+	1:32	0.8	38	90	15	6	0	1:8	1.8	100	—	—	Severe	ST SD	14 14	None	Steady improvement
23 M, 31	Portal cirrhosis	30	++	1:256 1:32	2.4 1.0	55	60	50	20	0	1:4	2.3	70	80	20	Moderate	ST	50	Rash, fever	Improved while on ST
24 M, 35	Portal cirrhosis	20 10	+	9.0 mg.*	—	70	—	—	10	0	0.2 mg.*	—	—	—	—	Moderate	SD	18	None	Died 4 months later of ruptured esophageal varix

25 M, 40	Portal cirrhosis	13	+	75 * 1.3	1.8	65	100	40	10	0	0·95* 60·8	3.3	75	30	0	Severe	SD SD	38 17	None	Improved while on SD; (chart 3)
26 F, 41	Bronchopneumonia; portal cirrhosis	110 60	0	0 2.9 mg.*	2.1	90	—	—	12	0	0 1.8 mg.*	2.0	—	60	25	Severe	SD	145	Agranulocytosis, fever	Liver status improved (chart 4)
27 M, 50	Pneumonia, SH; portal cirrhosis	7	0	1:128	—	60	70	50	10	0	1:128	2.1	85	40	20	Moderate	ST SD	20 23	None	Liver status unchanged; died 18 months later
28 F, 36	Postoperative pneumonia; biliary cirrhosis; c. b. d. stenosis	100	++	1.6 mg.*	1.2	50	—	—	100	++	3.6 mg.*	1.0	100	—	—	Severe	SD ST	20 19	None	No effect from SD; died of transfusion reaction
29 F, 43	Pneumonia; billiary cirrhosis, obstructive stenosis of c. b. d.	60	++	0	0.8	60	—	—	50	++	1:128	1.5	90	—	—	Severe	SD	30	None	Pneumonia improved; liver status unaltered (chart 5)
30 M, 50	Cholangitis; biliary cirrhosis; cholelithiasis	150	++	0	0.8	100	—	—	100	++	0	0.4	80	—	—	Severe	ST	64	None	Course unchanged
31 M, 53	Cholangitis; biliary cirrhosis; cholelithiasis	30 75	++	1:8	1.2	96	—	—	65 35	++	1:4	2.9	—	30	20	Severe	ST	30	Rash, fever	No effect; died 3 months later of ruptured varix
32 F, 62	Cholangitis, obstructive; biliary cirrhosis; carcinoma of gallbladder; pneumonia, Pn 33	80	++	1:256	0.1	70	—	—	7	0	1:2	2.3	95	—	—	Mild	SD	40	None	Improved by operation; died 3 months later of cancer
33 M, 58	Erysipelas; cirrhosis (? type); carcinomatosis	<10	0	1:16	0.7	67	30	20	<10	0	1:16	—	80	—	—	Moderate	ST	16	None	Infection improved; died 10 days after ST stopped
34 M, 18	Active R. H. D. with failure; C. P. C. of liver	60	0	1:16	1.5	27	—	—	10	0	1:32	—	50	80	40	Severe	ST	42	None	Died of R. H. D. 1 month after ST stopped
35 M, 46	Pyelonephritis, Hyp. H. D.; cardiac cirrhosis	10	0	1:32	—	100	70	5	8	0	1:4	—	80	60	50	Severe	ST	60	None	Pyuria cleared; rest of course unaltered
36 F, 46	Pyelonephritis, B. coli; cardiac cirrhosis	25	+ 0	1:128	1.0	100	—	—	13	0	1:128	1.5	65	35	30	Moderate	ST	48	None	Pyuria cleared rapidly; liver status unchanged
37 M, 26	Bronchopneumonia; R. H. D.; C. P. C. of liver	6	0	1:16	1.0	62	—	100	7	0	1.4	3.8	100	5	0	Moderate	SD	13	None	General improvement on ST

Abbreviations: (See table 1); Pn, pneumococcus, the number represents the type; SH, streptococcus hemolyticus; R. H. D., rheumatic heart disease; C. P. C., chronic passive congestion; Hyp. H. D., hypertensive heart disease; c. b. d., common bile duct.

* Watson method,[38] numbers represent milligrams per day.

† Given with equal amount of sodium bicarbonate.

the patient was obviously jaundiced and numerous spider telangiectases were seen about the head, the shoulders and the upper parts of the arms. There were also two pulsating angiomas on the forehead. His abdomen was distended by ascites, and the hepatic dulness extended 10 cm. below the costal margin. There was slight pitting edema of the legs and some hyperesthesia over the feet, and knee and ankle jerks were diminished. The significant laboratory data at that time (not shown in the figure) included the following values. icterus index, 25; plasma proteins, 5.2 Gm. per hundred cubic centimeters, of which 2.3 Gm. was albumin and 2.9 Gm. globulin; prothrombin, 55 per cent of normal, and excretion of hippuric acid, 1.8 Gm. (one week later it was only 0.34 Gm.).

The patient was given a diet high in protein and carbohydrate and low in fat. This was supplemented by corn syrup and a preparation of autolyzed yeast, and the patient was also given large doses of liver extract intramuscularly. His urinary output was low during the first four weeks and then began to increase gradually. After five weeks he had improved somewhat and was given sulfadiazine in doses of 1 Gm. every four hours for a week. The patient continued to improve while given the drug, and the ascites, which had remained stationary up to that time, began to clear with the onset of a pronounced spontaneous diuresis.

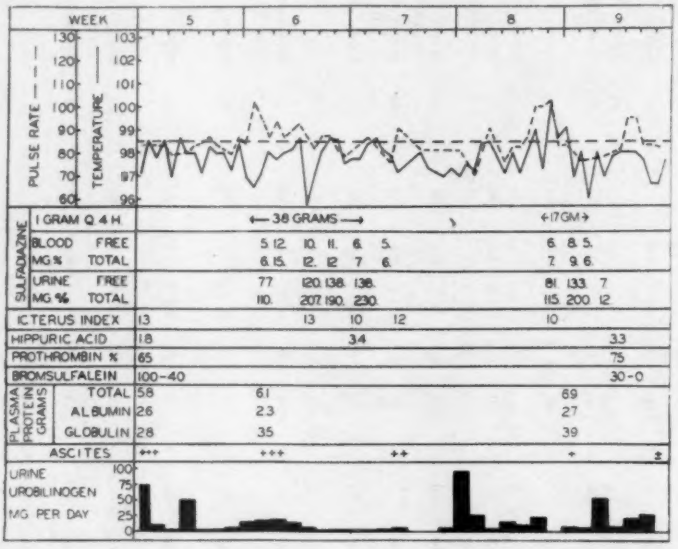

Chart 3.—Clinical chart and laboratory data in case 25 for the fifth to the ninth week in the hospital. A summary of the case history is given in the text (see also table 2).

There was also an appreciable increase in excretion of urobilinogen in the urine, such as is often seen during improvement in hepatic function in patients with portal cirrhosis. Two weeks later the patient was given a second course of sulfadiazine for three days for a mild infection of the upper part of the respiratory tract, and equally favorable results were obtained.

The improvement in this patient's condition was probably a reflection of a spontaneous remission with regeneration and healing of the liver and is probably in no way related to the administration of sulfadiazine. It is significant, however, that the favorable course was in no way altered by the chemotherapy. Of interest also is the fact that only from 60 to 70 per cent of the drug recovered in the urine was determined as "free" sulfadiazine. This would suggest that there was an essentially normal conjugation (acetylation) of the drug in this patient.[56]

Case 26 (chart 4).—A woman of 41 with a long history of alcoholism was admitted to the hospital after having symptoms of delirium tremens for three weeks. Nausea, vomiting, jaundice and dark urine had been present for five days. The patient was well nourished and moderately jaundiced. There were a few fine telangiectases over the forehead, the face and the neck. The edge of the liver was felt 4 cm. below the costal margin, and a small amount of ascites was made out. She was considered to have portal cirrhosis and was given

a diet high in protein and carbohydrate and low in fat. This was supplemented with yeast and parenteral injections of liver extract. During the patient's second week in the hospital, because of persistent fever and signs of bronchopneumonia, the administration of 1 Gm. of sulfadiazine every four hours was begun. The jaundice was subsiding at the time, and the icterus index had dropped from 110 to 40. Use of the drug was inadvertently continued for

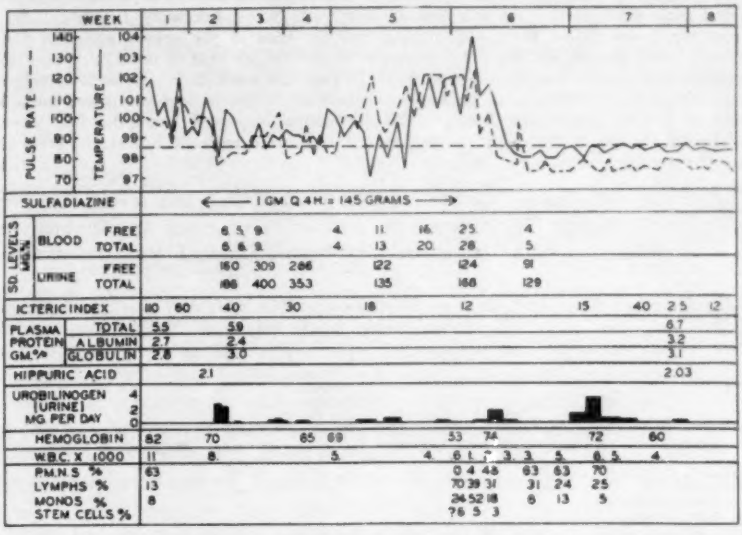

Chart 4.—Clinical chart and laboratory data in case 26. This case has been reported by Curry,[57] and a brief summary of the clinical observations is given in the text.

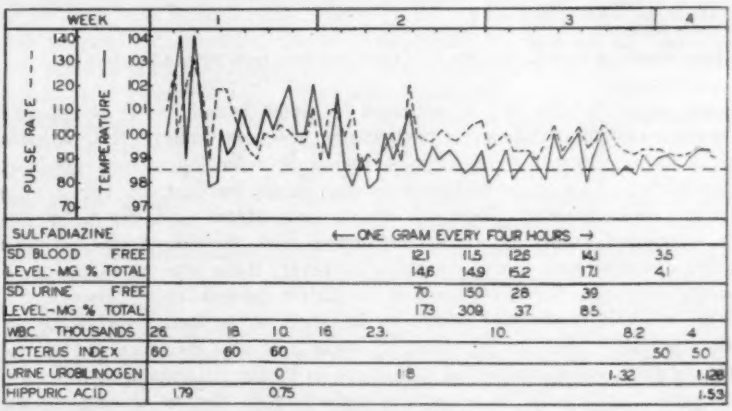

Chart 5.—Relevant data in case 29, a brief summary of which is given in the text.

twenty-four days, at the end of which time fever and agranulocytosis developed. Chemotherapy was then stopped, and the leukocyte count returned to normal in a few days. During the administration of sulfadiazine the hepatic function did not seem to be affected adversely and, in fact, continued to improve. There was a recurrence of the jaundice and a transient rise in the icterus index to 40 during the second week after use of the drug was stopped and

well after the temperature and leukocyte count had returned to normal. This case has been reported in greater detail by Dr. Curry.[57]

CASE 29.—A woman of 43 was admitted to the hospital because of fever, cough and bile-stained purulent sputum of several days' duration. She had had a cholecystectomy fourteen years previously and had become jaundiced one month after the operation. The jaundice had persisted in varying degrees ever since and was not improved after a laparotomy which was performed nine years later. At the time of entry she was moderately jaundiced, the liver edge was felt 7 cm. below the costal margin and the edge of the spleen was also palpable. The icterus index was 60, and the prothrombin level was 60 per cent of normal. The excretion of hippuric acid was 1.79 Gm. at that time and 0.75 Gm. one week later. Because of persistence of fever, leukocytosis and signs of pulmonary consolidation, the patient was given sulfadiazine in doses of 1 Gm. every four hours. The pneumonia improved promptly, but there was essentially no change in the jaundice and in the results of tests of hepatic function during or after the therapy (table 2 and chart 5).

Toxicity of Sulfonamide Compounds.—The important and severe toxic effects of sulfonamide therapy encountered in this series of cases are summarized in table 3 according to both the underlying hepatic disease and the drug used.

TABLE 3.—*Toxic Manifestations from Sulfonamide Compounds in Thirty-Seven Patients with Disease of the Liver*

Toxic Effect	Acute Hepatitis (13 Cases)	Portal Cirrhosis (14 Cases)	Biliary Cirrhosis (5 Cases)	Chronic Passive Congestion and Miscellaneous (5 Cases)	ST (21 Cases)	SD (21 Cases)	SP (2 Cases)	Total (37 Cases)
Fever alone	0	2	0	0	2‡	0	0	2
Rash and fever	2	2	1	0	4	1	0	5
Urinary tract (hematuria, colic, anuria, etc.)	0	3†	0	0	0	2	1	3
Nitrogen retention *	1	1	0	0	2	0	0	2
Agranulocytosis	0	1†	0	0	0	1	0	1
Total	3	9	1	0	8	4	1	13
Percentage of cases	23	64	20	0	38	19	50	35

For abbreviations see tables 1 and 2.
* Without hematuria, etc.
† One patient also had fever.
‡ 7 patients received both ST and SD; 2 of these had fever from ST and not from SD.

They are noted for the individual cases in tables 1 and 2. It is apparent that the serious complications were particularly frequent among the patients with portal cirrhosis. Renal complications, including retention of nitrogen, occurred in 4 patients. This high incidence is ascribable, in part, to the low urinary output of these patients, most of whom had edema and retention of water which responded rather poorly to treatment with diuretic drugs. In most of the other patients with portal cirrhosis, however, there was no evidence of renal irritation, although the daily output of urine ranged only between 500 and 1,200 cc. Administration of alkali in the form of sodium bicarbonate to these patients resulted in further retention of water and was therefore not as useful in preventing renal complications as it appears to be for patients who have a normal water metabolism.[58] In the remaining patients with chronic damage to the liver and in those with acute hepatitis, all the toxic effects of the sulfonamide compounds were less frequent than in the patients with portal cirrhosis, but the numbers of

57. Curry, J. J.: Acute Agranulocytosis Following Sulfadiazine, J. A. M. A. **119**:1502 (Aug. 29) 1942.

58. Peterson, O. L.; Goodwin, R. A., Jr., and Finland, M.: Observations on the Urinary Excretion of Sulfadiazine, J. Clin. Investigation **22**:659 (Sept.) 1943.

patients are too small to permit one to judge whether or not such effects were more frequent than in patients without damage to the liver.

Sulfathiazole and sulfadiazine were each used for 21 patients, including 7 who received both drugs either in succession or at different times. Toxic manifestations of the type listed in table 3 were twice as frequent during administration of sulfathiazole as they were during sulfadiazine therapy. Essentially the same relative frequency of toxic reactions has been noted from these two drugs in patients without disease of the liver. Of the 7 patients who received both drugs, 2 had fever from sulfathiazole only.

COMMENT

Although the number of cases studied is small, the results presented seem to be fairly consistent and warrant certain conclusions. The excellent results obtained after the administration of sulfathiazole and sulfadiazine (and probably also of sulfapyridine) to patients with acute hepatitis were striking. The successful treatment of the underlying infectious process produced rapid recovery from the damage to the liver. All the patients showed complete clinical recovery before they left the hospital, although 2 of them still showed evidence of residual damage, as indicated by tests of hepatic function. Acute hepatitis secondary to a bacterial infection calls for energetic treatment with full doses of such effective sulfonamide compounds as sulfathiazole and sulfadiazine instead of contraindicating their use. Complications of such chemotherapy appear to be no more frequent in this group than in patients with normal hepatic function.

In patients with chronic disease of the liver the results were not so striking. It is significant, however, that most of these patients had severe damage to the liver, and yet sulfathiazole or sulfadiazine did not aggravate their hepatic disease enough to produce measurable changes in the results of the functional tests that were employed. In the 2 patients who appear to have been made worse by the drugs, either the changes noted were coincident with the natural fluctuations in the disease or they were in some way related to the toxic manifestations of the drug. It is fair to conclude, however, that in cases of chronic damage to the liver, as in cases of acute hepatitis, sulfathiazole or sulfadiazine need not be withheld when their use is otherwise indicated. Some additional caution seems warranted in their use for chronic disease, particularly in order to insure an adequate urinary output.

In the patients with portal cirrhosis there are often associated diseases, such as alcoholism, faulty nutrition or specific vitamin deficiencies and water retention. The possibility of interference with the utilization of vitamins, such as nicotinic acid and thiamine, by drugs like sulfapyridine, sulfathiazole and sulfadiazine, because of certain chemical similarities, warrants some consideration.[59] It is doubtful, however, whether this factor is of any clinical significance, even in cases like the ones under discussion here.

The high incidence of toxic reactions to the sulfonamide therapy in patients with portal cirrhosis lends further weight to the contention that the liver is concerned in the "detoxification" of sulfonamide compounds. This process is probably different from the usual "conjugation" or "acetylation," such as one measures in determining the "free" and "total" sulfonamide compounds by the method of Bratton and Marshall.[54] The values obtained in blood and in urine by this method indicate relatively normal conjugation. The high incidence of renal complications, however, suggests the possibility that there is a failure to form soluble conjugates, such as glucuronates or ethereal sulfates, as noted by Scudi and his associates.[3]

59. Janeway, C.: The Sulfonamides: I. Their Mode of Action and Pharmacology, New England J. Med. **227**:989 (Dec. 24) 1942.

The frequency of other toxic manifestations, such as drug fevers, rashes and agranulocytosis, may also depend on the failure of some as yet unexplained form of detoxification by the liver.

Patients with hepatic dysfunction secondary to cardiac failure seemed to tolerate sulfathiazole and sulfadiazine about as well as those with acute hepatitis. The degree of hepatic dysfunction appeared to depend on the course of the underlying disease and apparently was unaffected by the chemotherapy. It has been pointed out previously that in cases of congestive cardiac failure complicated by bacterial infections, particularly if the respiratory tract is involved, the sulfonamide compounds may be extremely helpful.[60] With improvement of the infection, the cardiac decompensation responds more readily to rest and to digitalis therapy. Under these conditions, the accompanying diuresis often decreases the possibilities for renal complications.

It should be pointed out in closing that the possibility of damage to the liver by any of the sulfonamide compounds used in this series of cases has not been excluded by the observations presented. Such damage may occur under unusual conditions, for example, in patients with specific sensitiveness or idiosyncrasies, and when considerable retention of the drug occurs because of renal insufficiency or because excessive and toxic doses are employed either accidentally or for special purposes.

SUMMARY AND CONCLUSIONS

The effects of the administration of sulfonamide compounds, particularly sulfathiazole and sulfadiazine, on the clinical course and hepatic function have been studied for 37 patients with various types of damage to the liver.

In the patients with acute hepatitis associated with bacterial infections, the sulfonamide therapy was almost invariably associated with improvement in hepatic function which paralleled the improvement in the underlying infection.

In the patients with chronic damage to the liver hepatic dysfunction was not aggravated by administration of sulfathiazole or sulfadiazine. There was some improvement noted as a result of such therapy in cases in which bacterial infection was adding to the hepatic injury.

Severe toxic effects of sulfonamide therapy other than direct injury to the liver were unusually frequent in the patients with portal cirrhosis and were twice as common after sulfathiazole as after sulfadiazine.

It is concluded that the presence of damage to the liver should not be considered a contraindication to therapy with sulfathiazole or sulfadiazine in patients with bacterial infections against which these drugs are effective. Sulfadiazine is the drug of choice in such cases. Caution should be exercised in the administration of sulfonamide compounds to patients with severe portal (Laennec's) cirrhosis of the liver.

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469 Beacon Street, Boston.
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60. Finland, M.; Peterson, O. L., and Strauss, E.: Some Uses and Abuses of Chemotherapy in Pneumonia, New England J. Med. **225**:601 (Oct. 16) 1941.

RHYTHMIC PROPERTY OF THE HUMAN HEART

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The heart is a contractile organ, but it possesses important properties aside from that of contractility. The functions of rhythmicity, conductivity and irritability are also of fundamental importance in cardiac physiology. The clinician's attention is focused mainly on the contractile function of the heart, since the usual methods of examination, palpation of the apical impulse, auscultation of cardiac sounds and inspection of the heart by the fluoroscope, are means by which this property of the heart may be investigated. Furthermore, impairment of contractile efficiency is the basis for the most frequent manifestation of heart disease, congestive heart failure.

Rhythmicity is the property of stimulus formation, and since the heart is an automatic organ producing its own stimulus, it is obvious that this function is essential in the normal physiologic processes of the heart. If the rhythmic function is so reduced that no stimulus is produced, there is a sudden cessation of activity in a heart which may be entirely competent in its contractile power. This is the situation in the cardiac type of syncope associated with a hyperactive carotid sinus and in the ventricular standstill of heart block. On the other hand, there may be an increase in rhythmicity of certain portions of the heart. This leads to the development of ectopic rhythms and is related to the most serious cardiac arrhythmia, ventricular fibrillation. The mechanism of ventricular fibrillation is not definitely established, but there is evidence that the development of ectopic ventricular foci of rhythmicity plays an important part in the genesis of this arrhythmia. Wiggers [1] has demonstrated that an ectopic ventricular beat developing during a vulnerable phase in the heart cycle will consistently result in ventricular fibrillation. Ventricular fibrillation, either occurring spontaneously or induced experimentally, is preceded usually by a period of ectopic ventricular rhythm. Various drugs which increase ventricular rhythmicity, such as epinephrine or barium chloride, will induce ventricular fibrillation when administered in toxic doses or when given with other drugs. It has been demonstrated that ventricular fibrillation is the result of the synergistic action of epinephrine, a drug which increases ventricular rhythmicity, and a variety of substances, including chloroform [2] barium chloride,[3] benzene [4] and cyclopropane.[5]

From the University of Southern California School of Medicine.

1. Wiggers, C. J.: The Mechanism and Nature of Ventricular Fibrillation, Am. Heart J. **20**:399, 1940.

2. Levy, A. J., and Lewis, T.: Heart Irregularities Resulting from the Inhalation of Low Percentages of Chloroform Vapour, and Their Relationship to Ventricular Fibrillation, Heart **3**:99, 1912.

3. Rothberger, C. J., and Winterberg, H.: Ueber die experimentelle Erzeugung extrasystolischer ventrikulärer Tachycardia durch Accelleranreizung, Arch. f. d. ges. Physiol. **142**:461, 1911.

4. Nahum, L. H., and Hoff, H. E.: The Experimental Production of Ventricular Fibrillation and Its Prevention by β Methyl Acetyl Choline Chloride, Am. J. Physiol. **109**:78, 1934.

5. Orth, O. S.; Leigh, M. D.; Mellish, C. H., and Stutzman, J. W.: Action of Sympathomimetic Amines in Cyclopropane, Ether and Chloroform Anaesthesia, J. Pharmacol. & Exper. Therap. **67**:1, 1939.

It is clear that while a disturbance in contractile efficiency is the basis for the comparatively slowly developing congestive failure, sudden cessation of cardiac activity is a result of a disturbance in the rhythmic property of the heart.[6] Thus, a depression of cardiac rhythmicity leads to cardiac or ventricular standstill (hyperactive carotid sinus or heart block), while increased ventricular rhythmicity predisposes to ventricular fibrillation, which is generally accepted as the usual mechanism of sudden death due to a cardiac condition. It is therefore evident that the rhythmic property of the heart is of interest not only to the physiologist but to the clinician, so that he may have an intelligent approach to the therapy of disturbances of this function of the myocardium.

The exact nature of the heart's internal stimulus is unknown, and information concerning the factors influencing the rhythmic function is still incomplete. There are a number of theories suggesting a rhythmic development of a chemical or a physical state in the myocardium as the underlying process. The stimulus is developed in that part of the heart which is capable of producing these changes most rapidly. Ordinarily, this takes place in the sinus node. Other portions of the specialized tissue can produce the stimulus but are held in abeyance by the greater activity of the sinus node. A variety of factors can influence the rhythmic function, including temperature, hydrogen ion concentration and the presence or absence of certain inorganic salts. Particularly, as with other properties of the heart, the rhythmic function is influenced by the cardiac innervation, the parasympathetic nerves having a depressing action and the sympathetic nerves a stimulating effect.

The present report deals with observations on the rhythmic function of the human heart as influenced by modification of the cardiac innervation. The cardiac innervation was affected in the following manner: (1) parasympathetic stimulation mechanically by pressure on the carotid sinus and chemically by the use of mecholyl chloride (acetylbetamethylcholine chloride) and (2) sympathetic stimulation by the use of epinephrine and related compounds. In this report data regarding several phases of the subject are included. These consist of (1) the influence of age and sex and the presence of heart disease on cardiac inhibition by stimulation of the vagus nerve; (2) the efficiency of ectopic rhythmic centers of the human heart; (3) the distribution of the cardiac innervation to the rhythmic foci of the heart; (4) the action of drugs on reflex vagal inhibition of the heart, and (5) the influence of drugs on depressed and on increased rhythmicity of the human heart.

INFLUENCE OF AGE, SEX AND DISEASE ON VAGAL INHIBITION OF THE HEART

In carrying out observations on the effect of pressure on the carotid sinus in a large group of subjects over a period of years it was found that the cardiac response was influenced by several factors, including age, sex and presence or absence of cardiac disease.

Age.—Pressure over the carotid sinus usually depresses the heart rate slightly or not at all in persons below the age of 40. Between 40 and 50 there is an increase in the number of persons responding and in the intensity of the response. However, most of the hyperactive reactions in which a cardiac standstill was induced were obtained in subjects above the age of 50. In a previous report[7]

6. Nathanson, M. H.: Pathology and Pharmacology of Cardiac Syncope and Sudden Death, Arch. Int. Med. **58**:685 (Oct.) 1936.

7. Nathanson, M. H.: Site of the Exaggerated Sinus Caroticus Reflex, Proc. Soc. Exper. Biol. & Med. **29**:1037, 1932.

it was demonstrated that this increased response with increased age was not due to sclerosis of the carotid artery in the region of the carotid sinus but that it actually represented an increased reactivity of the vagus nerve. This confirms other observations indicating that vagal action increases with age. A more intense vagal effect has been noted in old cats as compared with young kittens.[8] In human beings after paralysis of the vagus nerve endings with atropine there is an increase in the degree of pulse acceleration up to the age of 30 and then a decrease, so that in old age there is little or no acceleration.[9] Gilbert [10] in human subjects also demonstrated an increased cardiac response to stimulation of the vagus nerve with increase in age, as did Sigler [11] in his studies.

Sex.—The response of the heart to pressure on the carotid sinus is much more marked in the male than in the female. In the female only a moderate slowing of the heart rate can be obtained even at advanced ages. In a period of five years, during which a prolonged cardiac standstill was noted in more than 100 male patients, this hyperactive reaction was noted in only 6 females. These observations indicate that in conditions, such as attacks of tachycardia of supraventricular origin, in which stimulation of the vagus nerve is desirable, an effect will more likely be obtained in a person of advanced years and of the male sex.

Presence of Cardiac Disease.—Before the discovery of the carotid sinus reflex many studies were carried out on the effect on the cardiac mechanism of pressure over the sheath of the carotid artery. This procedure was interpreted as a direct stimulation of the vagus nerve, and the studies were called "vagus pressure studies." There is some difference of opinion as to the significance of the various types of response, but there are several reports in the literature suggesting that a hyperactive cardioinhibitory response to pressure over the carotid sinus is frequently associated with coronary disease.[12] Braun and Samet [13] showed that the effect of stimulation of the vagus nerve was markedly increased in cats when branches of the left coronary artery system particularly were ligated. They concluded that damage to ventricular musculature increases the irritability of the vagus nerve. More recently, Sigler [14] concluded that coronary disease is the condition in which the reflex occurs with the greatest frequency and the highest degree of response. Early in my experience the great frequency of a hyperactive response in persons with coronary disease was noted. Of the first 40 subjects in whom a cardiac standstill was induced by pressure over the carotid sinus, there was evidence of coronary disease of the anginal type in 34. Of patients having coronary disease with angina, a hyperactive response was obtained in about one third. In the remaining two thirds the response was no more intense than may be obtained in normal subjects of the same ages. In young subjects and in females in whom a hyperactive response was obtained the incidence of coronary

8. Albutt, T. C.: Diseases of the Arteries and Angina Pectoris, London, Macmillan & Co., 1915.

9. Cushny, A. R.: Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1918.

10. Gilbert, N. C.: The Increase of Certain Vagal Effects with Increased Age, Arch. Int. Med. **31**:423 (March) 1923.

11. Sigler, L. H.: Clinical Observations on the Carotid Sinus Reflex, Am. J. M. Sc. **186**: 118, 1933.

12. Wenckeback, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, Wilhelm Engelmann, 1927, p. 128.

13. Braun, L., and Samet, B.: Vagusdruck und Koronargefass, Deutsches Arch. f. klin. Med. **161**:257, 1928.

14. Sigler, L. H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex, Arch. Int. Med. **67**:177 (Jan.) 1941.

disease was especially high. Sigler [14] stated that the more severe the coronary disease, the more apt the reflex is to occur and the greater is its degree. In my experience there did not appear to be any correlation between the severity of the disease and the presence or intensiy of the reflex. A hyperactive response was frequently noted in instances of milder disease and a negative reaction observed in cases of more severe disease. However, I agree with Sigler that a hyperactive reaction may be an aid in making a diagnosis of coronary disease in persons with suggestive signs and symptoms.

EFFICIENCY OF ECTOPIC RHYTHMIC CENTERS

It is well known that after the normal rhythmic center of the heart, the sinus node, is temporarily or permanently eliminated, the heart will continue to beat, since new rhythmic centers become active. Eyster and Meek [15] have shown that extirpation of the sinus node is followed by a rhythm arising either in the main portion of the auriculoventricular node or in an extension of this node around the mouth of the coronary vein. Cohn, Kessel and Mason,[16] after removing the sinus node in dogs, observed a transitory standstill of the heart, the duration varying from four seconds to three minutes, the interval being less than thirty seconds in most instances. The period of standstill represents the time required for some other portion of the heart to assume the pacemaking function. This variation in the time necessary for ectopic centers to function indicates a considerable variation in the rhythmic efficiency of ectopic centers in different animals. This type of experiment can be performed on many human subjects, since it is possible to eliminate the sinus node for relatively long periods by pressure on the carotid sinus.

In a series of electrocardiographic studies on elderly male subjects during application of pressure over the carotid sinus a hyperactive response was obtained in 34 subjects. After pressure over the carotid sinus the heart was deprived of its normal pacemaker for intervals varying from five to fifteen seconds. In 6 instances the elimination of the normal pacemaker was followed promptly by an ectopic rhythm of ventricular origin (fig. 1 *A*), so that a cardiac arrest did not occur. In 25 subjects a prolonged cardiac standstill was induced, as there was no spontaneous tendency for ectopic centers to become active during the period of inactivity of the sinus node (fig. 1 *B* and *C*). In most instances repeated performance of the experiment yielded a consistent response. In 3 subjects the reaction was variable, resulting in a cardiac standstill on one occasion and in a ventricular rhythm on repetition of the experiment. These observations indicate that there is a variation in different subjects in the rhythmic activity of ectopic centers and in most persons a relatively low efficiency of secondary rhythmic centers in the heart. This, undoubtedly, accounts for the variable reaction which follows a transition from normal rhythm to heart block. In those persons in whom the Adams-Stokes syndrome (ventricular stoppage) appears the rhythmic efficiency of the ventricular centers is low and a ventricular arrest precedes the development of rhythmic activity of the ventricular centers. In those persons in whom there is no ventricular standstill the rhythmic efficiency of the ventricular centers is such that they become active almost immediately after the ventricles are deprived of the stimulus from the auricles.

15. Eyster, J. A. E., and Meek, W. J.: Studies on the Origin and Conduction of the Cardiac Impulse, Am. J. Physiol. **61**:117, 1922.

16. Cohn, A. E.; Kessel, L., and Mason, H. H.: Observations on the Function of the Sino-Auricular Node in the Dog, Heart **2**:311, 1912.

DISTRIBUTION OF THE CARDIAC INNERVATION TO RHYTHMIC FOCI OF THE HEART

The influence of the vagus and the sympathetic nerves is not exerted equally on different portions of the heart. The sinus node is predominantly under the influence of the vagus nerve, although sympathetic fibers supply the node. Increases in heart rate due to exercise or to emotional excitement are a result primarily of lessening of vagal tone, rather than of an increase in sympathetic activity. The statement is generally made that the vagus nerves exert their influence predominantly on the auricles, while the sympathetic nerves exert their effect mainly on the ventricles. Physiologic studies on experimental animals indicate a variation in different species and in different animals of the same species. This variation in response has to do chiefly with the effect of the vagus nerve on the ventricles, and the reports are not entirely in agreement. Lewis [17] stated that in dogs in which the auriculoventricular bundle has been destroyed "a vagal influence on the ventricle is neither powerful nor invariable, while the sympathetics seem to possess a definite influence." Puddu,[18] however, concluded that the ventricular rate of dogs having complete heart block could be slowed by stimulation of the

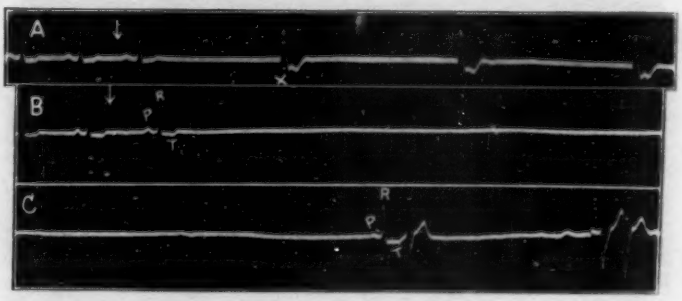

Fig. 1.—*A*, pressure on the carotid sinus (arrow) eliminates the sinus node, and a slow rhythm arising from an ectopic ventricular focus appears at *X*. *B* and *C* form a continuous strip showing a standstill of fifteen seconds induced by pressure on the carotid sinus. There is no tendency for ectopic rhythmic foci to become active. Cardiac activity is resumed only when the sinus node again functions.

vagus nerve. Lewis [17] also stated that while the vagus nerve has an influence on the fibrillating auricle, there is no effect on the fibrillating ventricle. Garrey and Bass [19] concluded that the ventricle of the frog is supplied with fibers from the vagus nerve, while that of the turtle is not. The sinus and atria of both animals are abundantly supplied with inhibitory fibers.

Technical difficulties have prevented anatomists from drawing accurate conclusions as to the distribution of the cardiac innervation. Recently, Nonidez [20] using a special histologic technic gave a detailed account of the distribution of the cardiac nerves in dogs. The parasympathetic fibers can be traced to their ter-

17. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1925.

18. Puddu, V.: Concerning the Action of Cardiac Nerves, Arch. f. d. ges. Physiol. **238**: 467, 1937.

19. Garrey, W. E., and Bass, G.: Effect of Acetylcholine on Frog's Ventricle, Am. J. Physiol. **119**:314, 1937.

20. Nonidez, J. F.: Studies on Innervation of the Heart, Am. J. Anat. **65**:361, 1939.

minations in the auricles, the bulk of these fibers ending in structures above the coronary sulcus. The sympathetic nerves are distributed as follows: The superior sympathetic nerve does not reach the heart proper, ending in the walls of the large arteries. The middle cardiosympathetic nerve is the largest one in the dog, supplying chiefly the ventricles. The inferior sympathetic nerve, when present, carries afferent fibers from various parts of the heart.

In the present studies data regarding the innervation of the human heart were obtained from the following observations: (1) the effect of pressure on the carotid sinus on ectopic beats arising in the auricles and ventricles; (2) the effect of pressure on the carotid sinus on the auricular and the ventricular rate in complete heart block, and (3) the effect of sympathetic stimulation (epinephrine) on cardiac rhythmicity.

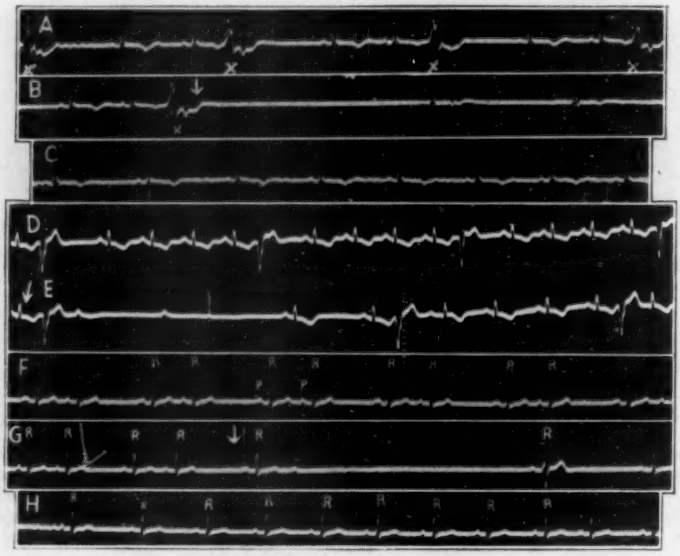

Fig. 2.—*A*, *B* and *C*, electrocardiograms made on 1 patient. *A*, consistent rhythm in this patient, cycles of two normal beats followed by a ventricular extrasystole (*X*). *B*, the effect of pressure on the right carotid sinus (arrow), followed in *C* by the abolition of the extrasystoles. *D*, consistent rhythm in another patient, cycles of four normal beats followed by ventricular extrasystole. *E*, an electrocardiogram made on the patient in *D*, showing the short standstill induced by pressure on the carotid sinus followed immediately by a return of the previous rhythm. *F*, coupled beats of auricular origin. *G*, a short standstill induced by pressure on the right carotid sinus (arrow) followed in *H* by elimination of the arrhythmia.

EFFECT OF PRESSURE ON THE CAROTID SINUS ON ECTOPIC RHYTHMS

Subjects were selected in whom a definite cardioinhibitory effect could be demonstrated by pressure on the carotid sinus during the period of normal rhythm and in whom ectopic beats occurred. Only those persons were studied in whom the ectopic beats appeared frequently and with definite consistency. Of 25 subjects in whom the ectopic beats were ventricular in origin, pressure on the carotid sinus eliminated the ectopic beats in 5 (fig. 2 *A*, *B* and *C*). In the remaining 20 the ventricular extrasystoles were not influenced (fig. 2 *D* and *E*). In 4

subjects in whom the ectopic beats originated in the auricle, pressure on the carotid sinus eliminated the ectopic beats (fig. 2 *F*, *G* and *H*).

EFFECT OF PRESSURE ON THE CAROTID SINUS ON THE RATES OF THE AURICLES AND THE VENTRICLES IN COMPLETE HEART BLOCK

It is usually stated that the ventricular rate in complete heart block is unaffected by such stimuli as increased activity and emotional excitement, indicating that the idioventricular center is much less under nervous control than is the sinus node. Puddu,[18] however, concluded that stimulation of the vagus nerve slowed the ventricular rate in experimental heart block in dogs. He attributed this effect to a transmission of the cholinergic material liberated in the auricles. Cullis and Tribe [21] demonstrated that sympathetic stimulation increases both the auricular and the ventricular rate in experimental heart block but that parasympathetic stimulation did not influence the ventricles. Gilchrist [22] concluded that in human beings the ventricles in heart block are influenced by activity and induced pyrexia and that the ventricular rate may be increased by atropine and epinephrine.

In the present study the effects of reflex stimulation of the vagus nerve were observed in 6 patients who had complete auriculoventricular dissociation. The

Effect of Pressure on the Carotid Sinus on the Auricular and the Ventricular Rate in Complete Heart Block

Patient	Auricular Rate	Ventricular Rate	After Pressure on the Right Carotid Sinus		After Pressure on the Left Carotid Sinus	
			Auricular Rate	Ventricular Rate	Auricular Rate	Ventricular Rate
N. S.	80	38	32	38	40	38
H. D.	88	30	45	30	62	30
M. P.	118	25	84	25	70	25
M. W.	100	34	76	34		
H. K.	64	33	33	33	36	30
C. W.	65	29	44	29		

results have been tabulated (see table). In each case pressure on the carotid sinus resulted in a definite slowing of the auricular rate. Pressure on the right carotid sinus was followed by a greater effect on the auricular rate in 3 of the 4 patients in whom both carotid sinuses were compressed. In 1 patient (M. P.) pressure on the left carotid sinus resulted in the more intense auricular inhibition. In none of the 6 patients did pressure on the right carotid sinus effect the ventricular rate. In 3 of the 4 patients in whom both carotid sinuses were compressed there was no effect on ventricular rate after pressure of the left carotid sinus, while in 1 patient (H. K.) there was a slowing of the ventricular rate from 33 to 30 beats per minute (fig. 3). This group of patients having two pacemakers working independently permits the study of the influence of parasympathetic stimulation on each pacemaker. The results support the concept that while the sinus node is profoundly influenced by parasympathetic stimulation, there is little or no effect on idioventricular centers in the human heart. This does not conclusively prove the absence of parasympathetic fibers to ventricular foci. It is possible that the degenerative lesion causing the heart block may also include the

21. Cullis, W. E., and Tribe, E. M.: Distribution of Nerves in the Heart, J. Physiol. **46**:141, 1913.

22. Gilchrist, A. R.: The Action of Atropine in Complete Heart Block, Quart. J. Med. **2**:483, 1933; The Effect of Bodily Rest, Muscular Activity and Induced Pyrexia in Complete Heart Block, ibid. **3**:381, 1934.

parasympathetic nerve endings, accounting for the lack of response to reflex stimulation of the vagus nerve.

EFFECT OF SYMPATHETIC STIMULATION ON CARDIAC RHYTHMICITY

It has repeatedly been shown that the rhythmic property of the heart may be disturbed by stimulation of the sympathetic nerves. In previous studies [6] it was found possible consistently to induce cardiac irregularities in human subjects by the administration of 0.1 mg. of epinephrine hydrochloride intravenously. The onset of the arrhythmia occurred within one minute after the administration of the drug, and the effect was usually completed within four or five minutes. In every case the ectopic rhythm induced was predominantly ventricular in origin. In some subjects an occasional auricular ectopic beat was noted as the effect of the drug was subsiding. At the height of the reaction the ectopic beats were entirely ventricular in origin.

The combined effect of parasympathetic and sympathetic stimulation on the rhythmic property of the heart has also been studied. Rothberger and Winterberg [3] demonstrated in dogs that stimulation of the right vagus nerve depressed the sinus node, resulting in a cardiac standstill. If at the same time the left

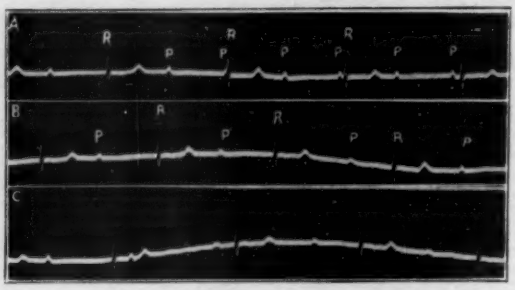

Fig. 3.—*A*, complete heart block, auricular rate 64 and ventricular rate 33. *B*, the effect of pressure on the right carotid sinus, reduction of the auricular rate to 33 and no change in the ventricular rate. *C*, the effect of pressure on the left carotid sinus, reduction of the auricular rate to 36 and the ventricular rate to 30.

sympathetic nerve was stimulated, the standstill was prevented by the development of new rhythmic centers in the ventricles. I have carried out similar studies on human subjects.[23]

Epinephrine and related compounds were administered to a large number of subjects in whom a cardiac standstill could be induced by pressure on the carotid sinus, and the pressure on the carotid sinus was repeated. In only an occasional instance was the standstill abolished by the restoration of the function of the sinus node. In most cases the standstill was abolished by the development of beats from a ventricular center (fig. 4). As an illustration, p-hydroxy-α-methylphenylamine hydrobromide (paredrine hydrobromide)—a sympathomimetic amine—was administered to 14 subjects in whom a cardiac standstill could be induced. In 7 instances the standstill was abolished by the development of a rhythm arising in or near the auriculoventricular node. In 3 subjects lower ventricular centers became active. In 1 subject the rhythm consisted of beats arising from the sinus

23. Nathanson, M. H.: Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus, Arch. Int. Med. **51**:387 (March) 1933; Further Observations on the Effect of Drugs on Induced Cardiac Standstill, ibid. **54**:111 (July) 1934.

node alternating with beats arising from an ectopic ventricular focus, while in 3 instances the sinus node retained its activity. These observations indicate that while the auricles may be influenced to some degree, the predominant effect of sympathetic stimulation is an increase in the rhythmicity of the ventricles.

It may be concluded that parasympathetic stimulation depresses the rhythmic property of the human heart, with the predominant effect on auricular rhythmic foci. In some persons, however, ventricular foci may be depressed. The effect of sympathetic stimulation is an increase in rhythmicity predominantly of the ventricles. It is apparent, then, that in states of increased cardiac rhythmicity

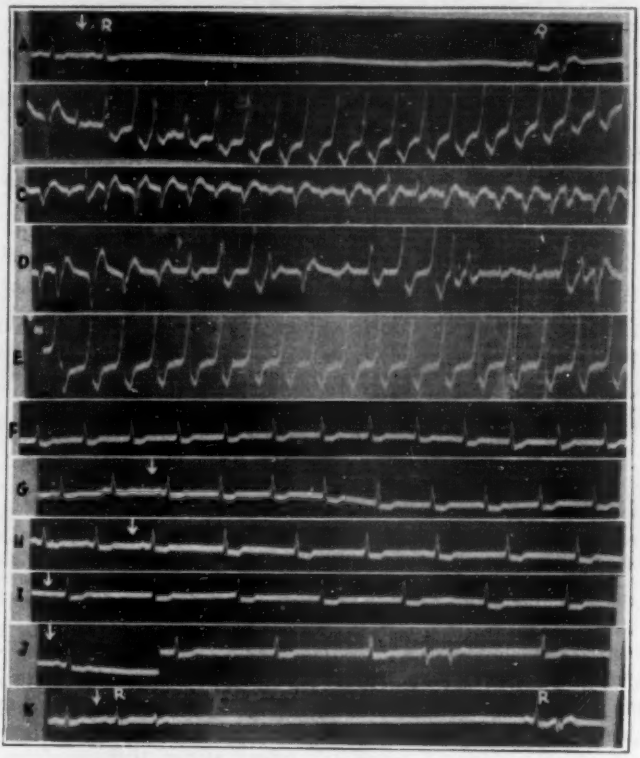

Fig. 4.—*A*, a cardiac standstill induced by pressure on the carotid sinus. The lower strips were made after the intravenous administration of 0.2 mg. of epinephrine hydrochloride. Note that at the height of the reaction (*B* through *E*) the beats arise from multiple, lower ventricular foci at a rapid rate. As the reaction subsides (*F* through *K*), the standstill is abolished by the development of a rhythm arising in the auriculoventricular node.

(ectopic tachycardias) reflex stimulation of the vagus nerve (pressure on the carotid sinus) is most likely to be effective when the ectopic focus is in the auricles. However, this procedure should also be attempted when the ectopic focus is ventricular, as the present observations indicate that parasympathetic stimulation depresses ventricular rhythmicity in some persons. It is also apparent that in states of depressed ventricular rhythmicity (ventricular standstill) sympathetic stimulation is indicated, since this predominantly influences the rhythmic function of ventricular foci.

ACTION OF DRUGS ON REFLEX VAGAL INHIBITION OF THE HEART

The action of drugs which act on the vagus nerve was studied. In 5 subjects in whom a prolonged cardiac standstill could be induced by pressure on the carotid sinus the administration of atropine sulfate, 2 mg. subcutaneously, abolished the effect (fig. 5). A comparison of figures 5 and 7 demonstrates the difference in the action of atropine and epinephrine. Both drugs abolish the standstill. Atropine, however, merely paralyzes the carotid sinus reflex, and pressure on the carotid sinus does not produce any effect. After medication with epinephrine the reflex continues to function, eliminating the sinus node, but the standstill is abolished by the development of a rhythm from a new pacemaker.

The effect of digitalis was observed in many subjects. Although not entirely consistent, an increase in the cardiac inhibition has been the usual reaction. It was noted frequently that in persons who do not show any response to pressure on the carotid sinus a definite reaction will follow digitalization. The results have not been sufficiently consistent to permit the use of the carotid sinus reaction as an accurate indication of digitalization. However, in many instances adequate digitalization was associated with a definite increase in the response to pressure

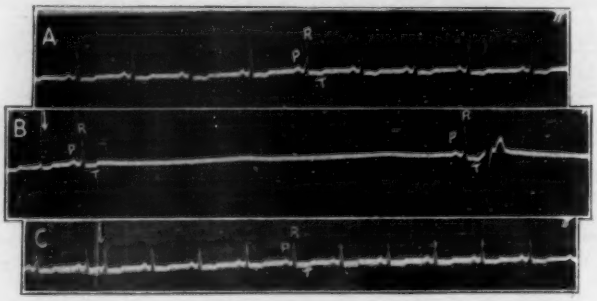

Fig. 5 (patient H. B., lead II).—*A*, a control electrocardiogram made before pressure was applied to the carotid sinus. *B*, cardiac standstill induced by pressure on the right carotid sinus (arrow). The interval *R-R* is seven and two-tenths seconds. *C*, the abolition of the reflex after the administration of 2 mg. of atropine sulfate.

on the carotid sinus. In 1 person having a hyperactive reaction the maximum period of standstill which could be induced on many trials was nine seconds. After digitalization a standstill of fifteen seconds followed pressure on the carotid sinus.

The administration of quinidine to subjects showing a hyperactive response was approached with caution. Since it has been shown that the drug depresses the myocardium and retards the rate of the sinus node in dogs,[24] it seemed possible that this might lead to a further delay in the return to activity of the sinus node, resulting in a seriously prolonged cardiac arrest. The drug was thus administered in small and increasing doses. The rather unexpected response after increasing the amount of quinidine sulfate to 2 Gm. in divided doses was a definite lessening of the vagus effect, so that the standstill was abolished (fig. 6). The explanation of this reaction was clear from the work of Lewis and his associates,[24] who demonstrated that in addition to the direct effect on the myocardium, quinidine possesses a definite vagoparetic action. Dale [25] showed that effect of the vagus

24. Lewis, T.; Drury, A. N.; Iliescu, C. C., and Wedd, A. M.: Observations Relating to the Action of Quinidine on the Dog's Heart, Heart **9**:55, 1921.

25. Dale, H. H.: Note on the Reversal of Vagus Action by Quinidine as Seen in the Heart of the Cat, Heart **9**:87, 1921.

nerve on the sinus node was not only eliminated by quinidine but that a reversal of the action of this nerve was obtained, with an acceleration of the sinus rate. The vagoparetic effect of quinidine undoubtedly accounts for its failure to be effective in slowing the sinus rate in simple tachycardia. This antagonism between the actions of quinidine and stimulation of the vagus nerve is of practical importance in the therapy of attacks of ectopic tachycardia. If quinidine is administered first and fails to terminate an attack, stimulation of the vagus nerve attempted subsequenly either mechanically or chemically will undoubtedly be ineffectual. If both therapeutic procedures are considered, it is apparent that stimulation of the vagus nerve should be attempted before quinidine is administered.

ACTION OF DRUGS ON CARDIAC RHYTHMICITY

Pharmacologic studies dealing with the influence of drugs on the rhythmic property of the heart are relatively few and are limited chiefly to laboratory studies on experimental animals. In view of variations in the reaction in different animal species, studies of the response of the human heart are of particular interest. Observations were carried out on the action of drugs on a state of depressed rhythmicity (induced by pressure on the carotid sinus) and increased rhythmicity

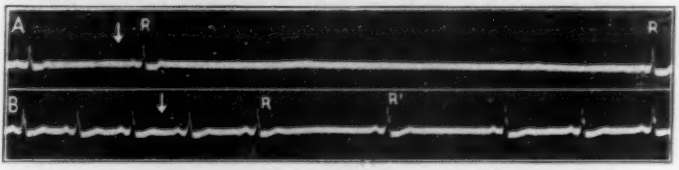

Fig. 6.—*A*, a standstill of nine seconds induced by pressure on the carotid sinus (arrow). *B*, the effect of pressure on the carotid sinus (arrow) after the administration of 2 Gm. of quinidine sulfate in divided doses.

(induced by intravenous injection of epinephrine) in a group of human subjects. A summary of these observations follows:

Effect of Drugs on Depressed Cardiac Rhythmicity.—The technic of these experiments was simple. Subjects, usually elderly men, were selected in whom a prolonged cardiac standstill could be induced consistently by pressure on the carotid sinus. After a control electrocardiogram was taken showing the induced standstill, the drug to be studied was administered and the procedure repeated at suitable intervals.[28] If a drug had no influence in increasing rhythmicity, the cardiac standstill was not affected. If a drug was effective, the cardiac standstill was abolished by the development of a rhythmic focus. The drugs selected for study were compounds which have been recommended in the therapy of cardiac standstill. These included epinephrine hydrochloride, ephedrine sulfate, barium chloride, calcium gluconate, digitalis, caffeine, nikethamide (a 25 per cent solution of pyridine betacarboxylic acid diethylamide), metrazol and thyroxin.

Of this group, it was found that the cardiac standstill could be consistently induced after the administration of barium chloride, calcium gluconate, digitalis, caffeine, nikethamide, metrazol and thyroxin, indicating that these drugs had no stimulating effect on cardiac rhythmicity. After epinephrine and ephedrine the cardiac standstill was consistently abolished, usually by the development of a new

rhythmic focus in the ventricles (fig. 7). A group of compounds related to epinephrine was then studied. This included ephedrine sulfate, dextroepinephrine bitartrate, cobefrine, adrenalone, epinine, synephrin tartrate, neo-synephrin hydrochloride, tryamine sulfate, hordenine sulfate, phenylethanolamine sulfate and paredrine hydrobromide. It was found that all of these compounds (sympathomimetic amines) increased cardiac rhythmicity leading to the prevention of abolition of cardiac standstill. Epinephrine was the most effective substance and paredrine the most active stable and orally active compound. These observations indicate that increase in the rhythmic property of the heart in those states in which this function is depressed or absent can be obtained only by drugs which have a specific pharmacodynamic action, that of stimulation of the sympathetic innervation of the heart. Drugs which do not possess this action are not effective and are not indicated in the treatment or prevention of cardiac standstill.

ACTION OF DRUGS ON INCREASED CARDIAC RHYTHMICITY

The rhythmic property of the heart was increased by the intravenous administration of epinephrine. As mentioned before, this procedure raises ventricular rhythmicity, so that for a time the normal rhythm is almost entirely replaced

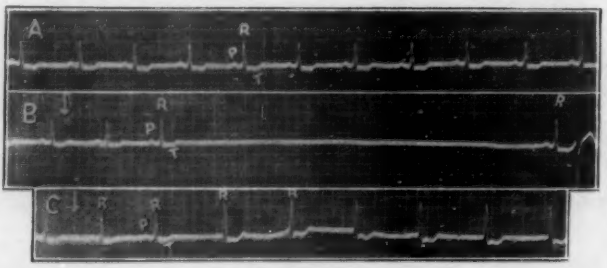

Fig. 7 (patient H. B., lead II).—*A*, a control electrocardiogram made before pressure was applied to the carotid sinus. *B*, a standstill induced by pressure on the carotid sinus. The interval *R-R* is seven and five-tenths seconds. *C*, the effect of pressure on the carotid sinus after the administration of epinephrine hydrochloride, 1 mg. subcutaneously. The standstill is abolished by the development of an idioventricular rhythm. These tracings were made on the same patient as those shown in figure 5, and the differences in the effect of atropine and of epinephrine are to be noted.

by beats originating in the ventricles. The experiments were carried out in the following manner: A control electrocardiogram was made and epinephrine hydrochloride, 0.1 mg., was injected intravenously. A continuous electrocardiogram was then made until the reaction subsided. Those subjects in whom frequent ventricular extrasystoles developed were used for further study. Several drugs were administered to these subjects, and at a suitable time the same dose of epinephrine was repeated. After the administration of ergotamine, potassium acetate and sodium amytal ventricular rhythms were induced by epinephrine similar to those observed prior to the administration of the drug. The reaction was modified in 10 subjects after the oral administration of quinidine sulfate, 1 to 2 Gm., in divided doses. In 8 instances the second administration of epinephrine did not induce extrasystolic rhythms, and in 2 subjects only an occasional ventricular extrasystole appeared.

It seemed important to investigate the effect of parasympathetic stimulation on increased cardiac rhythmicity. Mecholyl chloride was administered to 6 subjects in whom ventricular rhythms could be induced by epinephrine. The dose

of mecholyl chloride was 20 mg. injected subcutaneously. The second dose of epinephrine was administered five minutes later. In 5 of 6 subjects the ventricular rhythm was almost completely prevented after the administration of the mecholyl chloride (fig. 8). These observations are of interest since they indicate that a structure which receives little or no parasympathetic innervation (the human ventricle) is affected by a cholinergic substance. Garrey and Bass [19] concluded that acetylcholine has no influence on structures which do not receive parasympathetic innervation. However, Nahum and Hoff [4] prevented experimental ventricular fibrillation with mecholyl chloride, and these observers [26] also suppressed ventricular rhythms induced in cats by epinephrine hydrochloride with this drug. Starr [27] studied the effect of mecholyl chloride in only 1 patient having frequent ventricular extrasystoles, and the ectopic beats were greatly diminished in frequency. Although mecholyl has been suggested in the treatment of ectopic rhythms arising from a supraventricular focus, these observations suggest that it does have an influence on ventricular rhythmic foci.

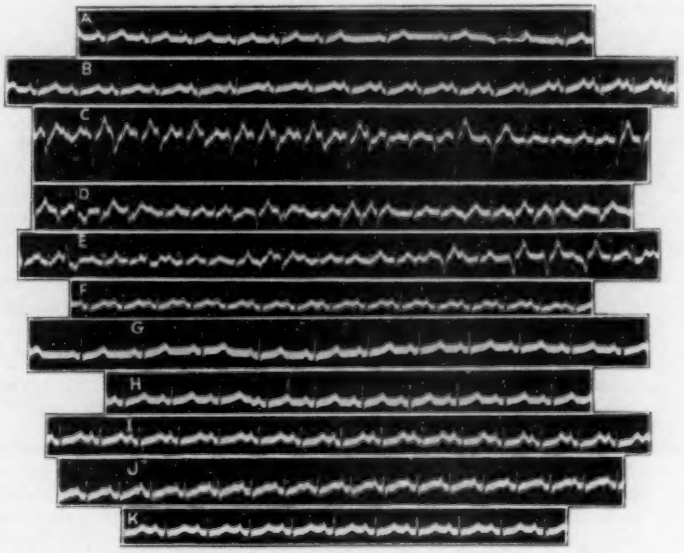

Fig. 8.—*A*, a control electrocardiogram made before the administration of epinephrine hydrochloride, 0.1 mg. intravenously. *B* through *F*, tracings made after medication with epinephrine hydrochloride. Ectopic ventricular beats from multiple foci appear in *C*, *D* and *E*. *G*, a control electrocardiogram made on the same patient before the administration of mecholyl chloride and epinephrine hydrochloride. *H*, tracing made after the administration of 20 mg. of mecholyl chloride. *I*, *J* and *K*, absence of ectopic beats after the administration of 0.1 mg. of epinephrine hydrochloride intravenously.

26. Hoff, H. E., and Nahum, L. H.: The Rôle of Adrenaline in the Production of Ventricular Rhythms and Their Suppression by Acetyl-β-Methylcholine Chloride, J. Pharmacol. & Exper. Therap. **52**:235, 1934.

27. Starr, I., Jr.: Acetyl-β-Methylcholine: IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm, Am. J. M. Sc. **191**: 210, 1936.

SUMMARY

The clinical importance of the rhythmic property of the heart is emphasized.

Physiologic and pharmacologic studies are reported on the rhythmic function of the human heart, carried out by modifying the cardiac innervation in the following manner: (1) parasympathetic stimulation by pressure on the carotid sinus or administration of mecholyl chloride, and (2) sympathetic stimulation by the administration of epinephrine and related compounds.

Reduction in cardiac rhythmicity by parasympathetic stimulation is more marked in males and in persons of advanced age. A hyperactive vagal inhibition of the heart is frequent in patients having coronary disease.

Studying persons in whom the sinus node can be eliminated for comparatively long periods leads to the conclusion that the rhythmic efficiency of ectopic centers of the human heart is low.

Parasympathetic nerves supply mainly rhythmic foci in the auricles, although the ventricles are influenced in some persons by parasympathetic stimulation. Sympathetic stimulation increases the activity predominantly of ventricular foci.

Digitalis increases reflex vagal inhibition of the heart in many persons. Atropine and quinidine have a vagoparetic action.

In states of depression or absence of the rhythmic function (cardiac or ventricular standstill) the only drugs which effectively increase cardiac rhythmicity are those which stimulate the sympathetic innervation (sympathomimetic amines).

Quinidine and mecholyl chloride tend to suppress the increased ventricular rhythmicity induced by epinephrine.

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DIAGNOSIS OF LIPOID PNEUMONIA BY ASPIRATION BIOPSY

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Within the past fifteen years lipoid pneumonia has been repeatedly reported in the literature. In almost every reported instance the diagnosis was a pathologic one made on autopsy material. In an occasional case the diagnosis was suggested by the history and the clinical findings, and the subsequent improvement followed discontinuance of the use of various oral and nasal oils.[1] In rare instances oil droplets have been visualized bronchoscopically and the diagnosis made in that way. It occurred to us that biopsy of material aspirated from the lungs, a procedure now in use in the study of obscure pulmonary and mediastinal lesions, would be of value, and we were successful in corroborating the suggested roentgenographic diagnosis of lipoid pneumonia in 5 of 10 cases examined in this way. As far as we can determine, this is the first report of lipoid pneumonia demonstrated by aspiration biopsy.

REPORT OF CASES

CASE 1.—G. B., a white man aged 82, when admitted to this hospital on July 28, 1941 had a history of rheumatoid arthritis of thirty years' duration. The history was obtained from the daughter, as the patient was hard of hearing. Swelling of joints and pain in both large and small joints marked the beginning of the disease. The course was that of chronic progressive atrophic arthritis involving gradually first the small joints and then the larger ones, including the vertebral joints. The patient became increasingly rigid, and during the last five years was in a wheel chair or confined to bed. He was treated with large doses of morphine sulfate for pain. After admission, the doses of morphine sulfate were gradually decreased, and finally the analgesic was given only sporadically. This patient was given liquid petrolatum, 1 ounce (30 cc.) daily, from the time of admission. On July 8, 1942 he had an episode of coughing with slight dyspnea and had a temperature as high as 103 F. Clinically, subcrepitant rales were heard over both bases of the lungs, but there was no dulness. The roentgen examination revealed infiltration of the lower lobes of both lungs, most evident in the mesial and basal portions of the lower lobe of the right lung. Extensive productive and fibrotic changes were present throughout the lower halves of both pulmonary fields. The pathologic observations impressed us as indicating bilateral bronchopneumonia superimposed on chronic pulmonary interstitial fibrosis (fig. 1 *A*).

The patient was treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and improved rapidly. Three weeks later he again had fever, cyanosis and cough. There was slight dulness with indefinite rales at both pulmonary bases. A roentgen study made at this time was not entirely satisfactory but showed no change from the previous study. Again sulfathiazole was given, and the patient improved after several days. One month later, in the course of our investigation of patients receiving liquid petrolatum, another roentgen study revealed findings identical with those of the original study. The observations now impressed

From the departments of pathology and roentgenology of the Jewish Sanitarium and Hospital for Chronic Diseases.

1. Tchekoff, I. G., and Ornstein, G. G.: Bronchopulmonary Disease Attributed to the Use of Intranasal Instillation of Oily Substances, Quart. Bull., Sea View Hosp. **1**:139-160 (Jan.) 1936. Greenwald, H. M.; Nathanson, L., and Steiner, M.: Chronic Pneumonia Associated with Nutritional Disturbances in Infants, Am. J. Roentgenol. **35**:454-467 (April) 1936.

us as indicating low grade chronic pneumonic infiltration, and the possibility of lipoid pneumonia was suggested. A subsequent aspiration biopsy confirmed the diagnosis of lipoid pneumonia (figs. 2 and 3).

The pneumonic lesion in case 1 was first demonstrated during the acute respiratory infection and persisted after the temperature subsided. The lesion was again demonstrated on the routine follow-up of patients' receiving large quantities of liquid petrolatum. It was then our impression that this patient had undergone an infection of the upper respiratory tract which did not alter the roentgen findings that were present at the first study.

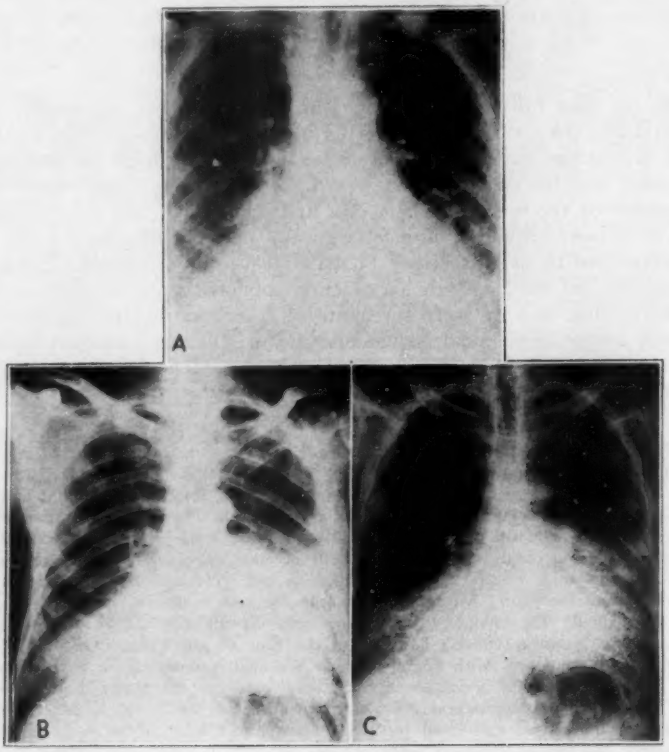

Fig. 1.—*A*, infiltration of the lower lobes of both lungs in case 1. The infiltration is most intense in the mesial and basal portion of the lower lobe of the right lung. Note the diffuse fibrosis. *B*, consolidation of the lower lobes of both lungs in case 2, most dense in the mesial portions of the lung fields. *C*, essentially normal bronchi; shown by passive bronchoscopy in case 2.

CASE 2.—S. W., a 58 year old man, was admitted to this hospital on Sept. 11, 1931. Six weeks prior to his admission he had suffered cerebral thrombosis resulting in left hemiplegia. Prior thereto the patient had apparently been in good health. Until Feb. 19, 1940 he was ambulatory. On that day he experienced cerebral thrombosis resulting in paresis of the right side with aphasia. The picture was that of pseudobulbar palsy. There was great difficulty in swallowing, and his speech was dysarthric. The patient had been receiving liquid petrolatum since 1935, when he complained of constipation following acute enteritis with diarrhea. He received about 1 ounce (30 cc.) of liquid petrolatum two to three times weekly for about three years. Since the second cerebral episode (February 1940)

he had been taking 1 ounce of liquid petrolatum every other night. In August 1940 he had an episode of coughing and dyspnea with temperature ranging from 101 to 103 F. Clinically, there was no dulness, and few subcrepitant rales were heard over the bases of both lungs. A roentgenogram taken at that time revealed dense consolidation of the mesial and basal portion of the lower lobe of the right lung and the lower half of the left lung (fig. 1 *B*). The patient was given sulfonamide compounds, and the fever and other symptoms soon subsided. A roentgenogram taken two months later revealed the same changes, and passive bronchography showed no evidence of bronchiectasis (fig. 1 *C*). The infiltration was then regarded as interstitial or alveolar in type, and we suggested the diagnosis of lipoid pneumonia. A roentgenogram taken on Nov. 3, 1942 revealed essentially the same conditions as the one previous. An aspiration biopsy revealed the typical cells of lipoid pneumonia.

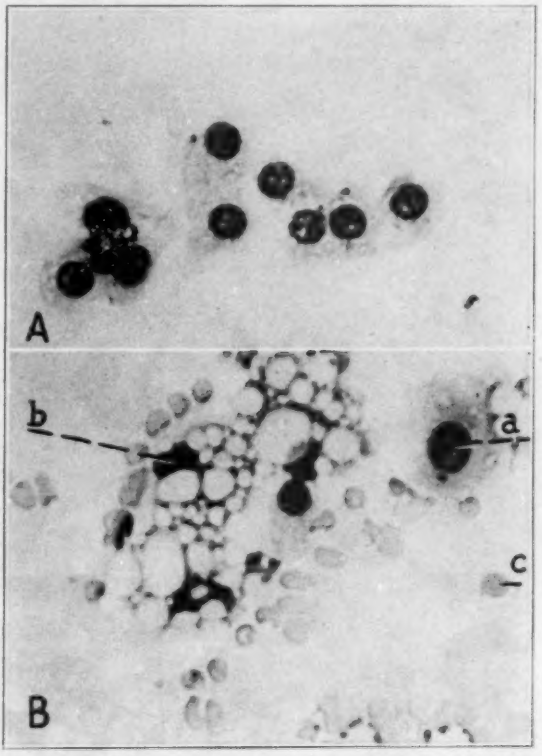

Fig. 2.—*A*, groups of monocytic cells in the beginning stage of phagocytosis. The pale round cells at the right are red blood cells. *B*, cells aspirated from the lungs: (*a*) macrophages beginning to phagocytose the oil droplets; (*b*) groups of macrophages in a later stage of inhibition; (*c*) red blood cell.

The first roentgen study in case 2 was made because of an acute pulmonary episode which clinically suggested a bilateral pneumonic process. The final roentgen study, made more than two years later, showed no appreciable change, indicating that the infection was low grade. Because the lesion was of a bilateral basal type the thought was entertained that this was a low grade aspiration type of pneumonia, possibly lipoid in nature. It is impossible to state from the roentgenograms per se whether this patient had superimposed bronchopneumonia, since there was no change of the pulmonary findings on subsequent films.

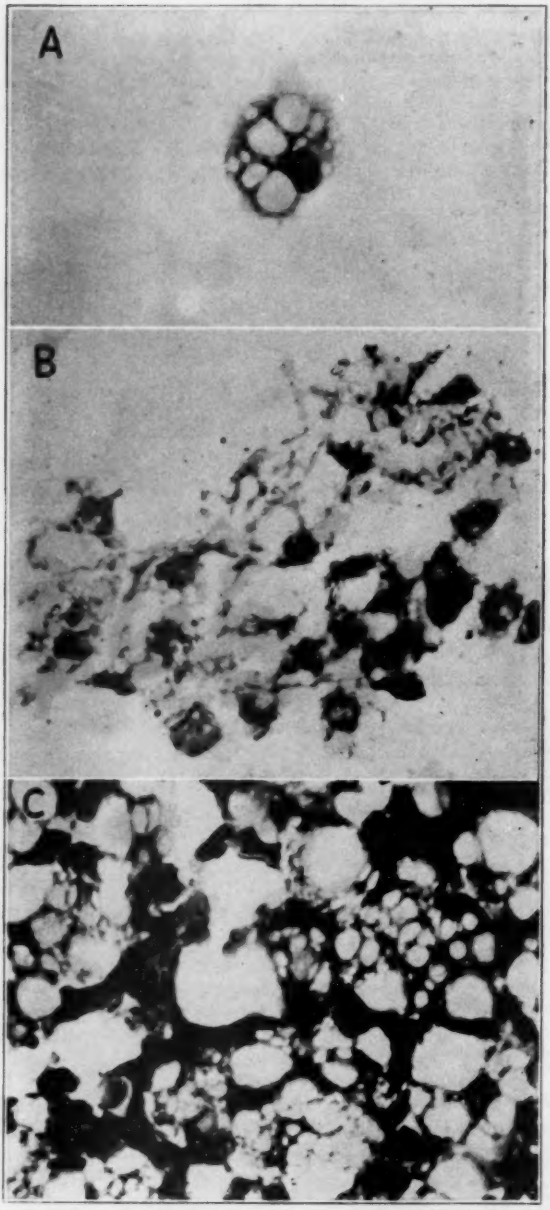

Fig. 3.—*A*, single lipophagic cell. Note the fine subdivisions of the phagocytosed oil droplets. *B*, stage of disintegration of macrophages. *C*, meshwork of fibrotic tissue with entrapped oil droplets. Formation of giant cells can also be seen.

CASE 3.—J. P., a 57 year old white woman, was admitted to the hospital on Nov. 30, 1937. About eleven years prior to admission it was accidentally discovered that she had hypertension. She had been in fairly good health, complaining only of occasional dizziness. Six weeks prior to admission she had a cerebral episode resulting in left hemiplegia. Speech returned almost completely within two weeks. On admission to this hospital, redundant colon and secondary megacolon were diagnosed. The patient was given liquid petrolatum, 1 ounce (30 cc.) daily. A routine roentgen examination of the chest at that time (Dec. 16, 1937) gave entirely negative results (fig. 4 *A*). The patient was bedridden at all times. During her stay there were many episodes of fecal impaction, and oil enemas had to be given and manual extraction resorted to. To prevent impaction, many cathartics in addition to liquid petrolatum were given. The patient was dull mentally, but her speech was normal and the ninth and tenth cranial nerves were intact. A routine roentgen examination made Dec. 14, 1942 showed irregular coalescence and patchy infiltration of the lower lobes of both lungs. The lesions on both sides were extensive (fig. 4 *B*).

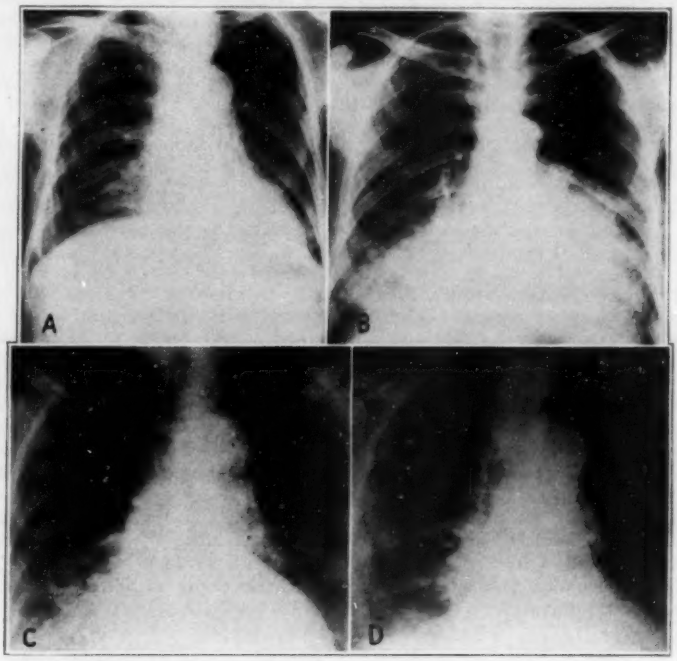

Fig. 4.—*A*, normal chest of the patient in case 3 on Dec. 16, 1937. *B*, chest of the same patient on Dec. 14, 1942. Note the dense mottled consolidation involving the lower lobes of both lungs, particularly evident in their mesial portions. *C*, irregular infiltration involving the basal portion of the lower lobe of the right lung in case 4. The infiltration is particularly intense in the mesial and supradiaphragmatic portions. *D*, dense infiltration adjacent to the border of the heart and patchy infiltration, fibrotic in character, extending through the lower lobe of the right lung in case 5.

In case 3 we were able to follow the patient roentgenographically for a period of five years. The original roentgenographic study of the chest revealed no abnormality. The final one, made during a routine examination of patients receiving considerable quantities of liquid petrolatum, showed the pathologic roentgenographic features described. There were no clinical symptoms or physical signs referable to the chest. A diagnosis of lipoid pneumonia was suggested from the roentgen

studies, and an aspiration biopsy revealed typical vacuolated cells in great masses, patched together. A small amount of fibrosed pulmonary tissue could also be seen on the smears.

CASE 4.—S. A., a white woman aged 58, was admitted to this hospital in May 1934. Five years prior to admission she had been operated on for disease of the gallbladder; three years later she was operated on because of adhesions. During the last ten years she had suffered from frequent attacks of asthma and of paroxysmal tachycardia. A diagnosis was made of coronary sclerosis, hypertensive heart disease and postoperative adhesions. The patient had received 1 ounce (30 cc.) of liquid petrolatum daily since 1934. Many indefinite rales were heard at the bases of the lungs, but there was no dulness. During the asthmatic attack many musical rales were audible throughout both lungs. Signs of cardiac decompensation were not present. A roentgenographic study of the chest in April 1938 showed no abnormality. A study of the chest made Nov. 13, 1942 (fig. 4*C*) during a routine investigation of patients receiving liquid petrolatum over a period of time showed a dense irregular infiltrative lesion involving particularly the mesial portion of the lower lobe of the right lung and the most dependent portion of the right lung above the diaphragm. Because of the negative pulmonary history and the negligible physical signs, the diagnosis of low grade aspiration pneumonia, possibly of a lipoid type, was suggested. Repeated biopsies revealed the typical cells of lipoid pneumonia in various stages.

Although the roentgen studies and the aspiration biopsy clearly indicated the presence of lipoid pneumonia, the patient was entirely symptom free except for long-standing asthma. The physical findings were those attributable to the asthma.

CASE 5.—B. S., a white woman aged 66, was admitted to this hospital in October 1941. She gave a history of hypertension of long standing. In 1916 she had Bell's palsy, which improved on electrical treatment. In 1935 she suffered a cerebral insult resulting in right hemiplegia without aphasia. During that year mild diabetes was discovered. In May 1941 she had a cerebral insult without loss of consciousness, increasing the paralysis on the right side. Physical examination revealed severe hypertension, an aneurysm of the internal carotid artery of the neck and right hemiplegia without aphasia. She had been confined to bed since the second cerebral accident. She had been taking liquid petrolatum for several years because of chronic constipation. A barium sulfate enema revealed diverticula of the large bowel. During her stay in the hospital she received about 1 ounce (30 cc.) of liquid petrolatum daily. Again, during the routine investigation of patients receiving liquid petrolatum over a long period, a roentgenogram (fig. 4*D*) of the chest disclosed a dense infiltrative lesion involving the mesial portion of the lower lobe of the right lung adjacent to the heart with patchy areas of infiltration throughout the remainder of the lobe, particularly over the diaphragm. A densely thickened pleura was present along the lower axillary portion of the lung. Because of similar findings in other patients, we again suggested the diagnosis of low grade aspiration pneumonia, and an aspiration biopsy disclosed a lipoid type of pneumonia.

COMMENT

The positive diagnosis of lipoid pneumonia, or, to use a better term, oil aspiration pneumonia, has in the past been a pathologic one. The condition was studied on autopsy material [2] and on animal material in which lipoid pneumonia had been produced experimentally.[3] The various reactions of the lung tissue to different oils were first described by Pinkerton,[3a] and he enumerated the following pathologic responses: (*a*) Animal oil produces fibrosis and giant cell formation in the lung together with necrosis and edema; the latter two depend on the amount of free fatty acids present in the oil. (*b*) Vegetable oils (e. g., poppyseed oil), with the exception of chaulmoogra oil, produce practically no reaction. (*c*) Liquid

2. Laughlen, G. F.: Studies on Pneumonia Following Nasopharyngeal Injections of Oil, Am. J. Path. **1**:407 (July) 1925. Rabinovitch, J., and Lederer, M.: Lipoid Pneumonia, Arch. Path. **17**:160-168 (Feb.) 1934.

3. Pinkerton, H.: (*a*) The Reaction of Oils and Fats in the Lungs, Arch. Path. **5**:380-401, (March) 1928; (*b*) Oils and Fats: Their Entrance into and Fate in the Lungs of Infants and Children, Am. J. Dis. Child. **33**:259-285 (Feb.) 1927.

petrolatum (mineral oil) produces a macrophagic reaction with giant cell formation and fibrosis. The largest series of cases was published recently by Freiman and associates.[4] They reported 47 cases—41 which were taken from autopsy material and 6 in which the clinical diagnosis was made on presumptive evidence that warranted the diagnosis of lipoid pneumonia.

In our investigation we were primarily concerned with finding and evaluating a means of establishing the diagnosis of lipoid pneumonia during life. While pursuing this aim, we were able to observe the evolution of the process hitherto described on autopsy material only.

The histologic response of the lung to liquid petrolatum can be briefly summarized as follows: The droplets of oil entering the alveolar space act as a chemical mechanical irritant. Soon monocytic cells (fig. 2 *A*) appear and phagocytose the oil droplets. At first these cells take on a foamy appearance (fig. 2 *B*); later, in the course of imbibition, they resemble ordinary fat cells. At first round or oval, they become bulky and of irregular contour, depending on the number of oil droplets phagocytosed. The latter press the nucleus toward the periphery but retain their subdivision for a long time (fig. 3 *B*), possibly until the cell disintegrates (fig. 3 *B*). In this stage one finds giant cells and fibrosis—briefly, a histologic response commonly seen in the presence of a foreign body. As time goes on the fibrosis increases, and the oil of the disintegrated lipophages becomes entrapped in the meshwork of the fibrous tissue (fig. 3 *C*). If the amount of fat is considerable, and if fibrosis and giant cell formation are so abundant as to form a tumor, one speaks of a paraffinoma. The latter stage was not encountered in our series of cases.

Since the aspiration of the oil in most cases extends over a period of years, one is apt to find all the various stages of lipoid pneumonia present concomitantly. This has been proved on autopsy material as well as in our series of aspiration biopsies. Ten patients having a history of taking liquid petrolatum over a period of years were investigated. The patients were selected at random, but the presence of dysphagia or dysarthria or the fact that the patient was bedridden guided us in the choice. After roentgen films of their chests had been taken, those with positive roentgen findings were subjected to aspiration biopsies. Repeated biopsies were made in all cases in order to exclude any doubtful findings and to demonstrate the various stages of the pathologic process. A positive result of an aspiration biopsy was considered of significance but a negative one did not necessarily rule out the diagnosis.

The following technic was used:

The pulmonary lesion was carefully localized in each instance by means of roentgenograms. As a rule, the posteroanterior and lateral views sufficed. Fluoroscopic control was not necessary but may be used if the patient's condition permits. The skin was anesthetized with 2 cc. of 1 per cent solution of procaine hydrochloride. A 20 cc. syringe with a spinal tap type of needle was used. The plunger of the syringe was withdrawn to the 5 cc. mark, and the needle was inserted into the localized area, penetrating as much as 9 to 10 cm., depending on the site of the lesion. Once the needle was inserted, we attempted to withdraw the plunger to make sure the point of the needle was not in a blood vessel or a bronchus. The plunger was then forced down to the bottom of the syringe, ejecting the contents of the lumen of the needle, so as to remove any tissue that may have entered in the passage through the chest wall. The position of the needle was then changed slightly either by withdrawing the needle or by altering its direction. The plunger was then slowly withdrawn with aspiration of as much tissue as possible. Finally, the needle was withdrawn,

4. Freiman, D. G.; Engelberg, H., and Merrit, W. H.: Oil Aspiration Pneumonia in Adults, Arch. Int. Med. **66**:11-38 (July) 1940.

and the contents were forcefully ejected on four slides. One slide was regarded as an ordinary blood smear and stained with Wright's stain for ten minutes. The other three were treated with various fat stains for the identification of the type of fat.

The histologic character of the smear depended on the area from which the tissue was aspirated. Usually it was loaded with red blood cells and scattered phagocytic cells; the latter were often in groups of two to three. Occasionally a smear was obtained which contained a rather small number of the macrophages, and occasionally the material consisted of clumps of macrophages, fat droplets, fibrocytes and giant cells. The presence of macrophages in the smear was considered of positive diagnostic value. The fat stains confirmed the character of the phagocytosed material. Because of the rather "blind" selection of the area for aspiration biopsy, it is difficult to state how far the lesion has progressed. Where, however, the roentgen film shows a lesion resembling a tumor, the aspiration should be done under fluoroscopic control so as to obtain tissue directly from the tumefied area. Because of the chronicity of this type of lesion and the probable obliteration of the pleural space, we did not hesitate in using this method of diagnosis. No untoward effects were noticed in any of our patients except 1, who expectorated a small amount of blood. A half-grain (0.03 Gm.) of a codeine salt usually sufficed to control the pain and the anxiety.

Roentgenographically the pulmonary lesion was not characteristic, but the infiltration as a rule involved the lower lobes of both lungs and particularly the lower lobe of the right lung. The mesial portion of the latter lobe adjacent to the heart was the earliest site of involvement. The infiltration then spread to the dependent portions of the lobe above the diaphragm. The process varied in character from patchy infiltration to dense consolidation with fibrosis. There was little change in the lesion over prolonged periods.

SUMMARY AND CONCLUSIONS

Ten patients who had a history of receiving liquid petrolatum for many years and who had suggestive roentgenograms pointing toward the diagnosis of lipoid pneumonia were investigated by means of aspiration biopsies. The material aspirated from the lungs of 5 of the 10 patients gave smears containing the characteristic lipoid macrophages.

One patient had difficulty in swallowing. Two had hemiplegia (without dysphagia). Four were bedridden or confined to wheel chairs.

The roentgenographic studies showed the pulmonary lesions confined to the mesial portions of the lower lobes of both lungs and particularly to the lower lobe of the right lung.

The positive smear can be regarded as diagnostic. A negative smear does not rule out the diagnosis.

The technic of an aspiration biopsy of the lung is outlined. No serious ill effects were encountered following this procedure.

The evolution of the pathologic process was followed during life by means of such biopsies.

Drs. A. M. Rabiner, C. Solomon, H. Mandelbaum and L. Lowe, in whose services the cases reported in this paper were studied, gave us permission to report these cases.

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SYPHILIS

A REVIEW OF THE RECENT LITERATURE

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The material for this article has been selected from publications which have appeared from July 1942 to June 1943. As in previous reviews,[1] it has been necessary rigidly to select material, excluding comparative serologic studies and most case reports. The number of European journals available for review is negligible, but the deficit is offset by the growing interest of Latin American authors in the subject. Because the war has focused attention on the prevention of syphilis, especially among the armed forces, there is an increased number of articles on control of the disease.

HISTORY OF SYPHILIS

A fascinatingly readable account of syphilis as disclosed in the writings of the Elizabethan playrights and pamphleteers has been contributed by Zimmermann.[2] Important historical points are clarified and a vivid picture of daily life in Renaissance Europe depicted. The customs of these times, crude, rough, even bawdy, are portrayed in such a manner as to present not only a clinical but also a public health picture of syphilis as seen by the physicians and public health officials of the day.

Elizabethan England is depicted through the words of Shakespeare, Johnson and the lesser lights. The problems of today (prostitution, pandering, high incidence of syphilis, clinical syndromes of the disease) also confronted physicians centuries ago. Zimmermann is more than a competent historian; he is an excellent entertainer. In his stories of syphilis of a century ago the physician will find information and pleasurable relaxation.

According to Poirier,[3] syphilis was brought to Canada by a sailor who accompanied Jacques Cartier on his first voyage in 1534. A notable epidemic

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1. (*a*) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1935. (*b*) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936; (*c*) **60**:887 (Nov.) 1937. (*d*) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **62**:1029 (Dec.) 1938. (*e*) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, ibid. **64**:1053 (Nov.) 1939. (*f*) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **66**:1112 (Nov.) 1940. (*g*) Mohr, C. F.; Padget, P.; Hahn, R., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **69**:470 (March) 1942. (*h*) Reynolds F. W.; Mohr, C. F., and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **70**:836 (Nov.) 1942.

2. Zimmermann, E. L.: (*a*) Syphilis and the Elizabethan Playrights and Pamphleteers, Am. J. Syph., Gonor. & Ven. Dis. **27**:78 (Jan.) 1943; (*b*) **27**:226 (March) 1943.

3. Poirier, P.: Histoire de la syphilis en Amérique, J. de l'Hôtel-Dieu de Montréal **1**:64 (Jan.-Feb.) 1943.

occurred about the Bay of St. Paul after the introduction of syphilis into the area by a group of soldiers in 1773, and subsequently spread along the St. Lawrence and Ottawa rivers and throughout the entire province of Quebec. The true nature of the malady was not recognized by a group of eminent physicians sent by the government to investigate. It was identified as syphilis in 1785 by Philippe Louis Francois Badelard, whose monograph describing his findings is said to have been the first medical publication in Canada.

The mal de la Baie St.-Paul has not received the same publicity as the massacre of Lachine or the deportation of the Acadians, but its repercussions were more profound and more pernicious than any other situation faced by the struggling young colony.

SPIROCHAETA PALLIDA

Spirochaeta Pallida in the Electron Microscope.—Knowledge of the morphology of Spirochaeta pallida has been furthered through the use of the electron microscope, capable of obtaining very high magnification. Unfortunately, technical difficulties necessitate immobilization and desiccation of the organism, so that some distortion is present. Wile, Picard and Kearny [4] note that as seen in the electron microscope S. pallida undergoes distortion, lengthening and flattening of the coils ascribable to the technic of preparation. A complete and continuous membrane-like structure about the organism was demonstrated, as were knoblike structures of fairly uniform density which seemed to be integrated with the body of the organism.

Although unable to see flagella on S. pallida under the electron microscope by direct inspection of the fluoroscopic screen, Wile and Kearny [5] note that flagellum-like processes may be demonstrated in enlarged photographic reproductions. These processes were found frequently enough to justify the assumption that they are an integral part of the organism.

In addition to the demonstration of granules, spherical bodies and flagellum-like filaments, Morton and Anderson [6] have made certain observations on the division of spirochetes. In the electron microscope, these workers have noted initial constriction of the spirochetal body, leading eventually to two spirochetes held together by a tenuous membrane. After separation of the organisms at this point, the thin membrane persists as a terminal filament.

Cultivation of Spirochetes.—Kast and Kolmer [7] have been unable to cultivate S. pallida on an artificial medium containing normal rabbit testicular tissue after the method of Morrison (to whom in 1941 a government patent was issued covering the procedure). It is a remarkable commentary on the United States Patent Office that a patent can be issued for claimed bacteriologic success in this difficult field to a physician who has commercialized "vaccines" and "serums" for syphilis, tuberculosis and, of all things, hypertension. Apparently one can patent anything, whether or not it works.

The differentiation of S. pallida from other spirochetes which so frequently are found in the oral cavity, especially when dental hygiene is poor, is a matter of

4. Wile, U. J.; Picard, R. G., and Kearny, E. B.: Morphology of Spirochaeta Pallida in the Electron Microscope, J. A. M. A. **119**:880 (July 11) 1942.

5. Wile, U. J., and Kearny, E. B.: The Morphology of Treponema Pallidum in the Electron Microscope: Demonstration of Flagella, J. A. M. A. **122**:167 (May 15) 1943.

6. Morton, H. E., and Anderson, T. F.: Some Morphologic Features of the Nichols Strain of Treponema Pallidum as Revealed by the Electron Microscope, Am. J. Syph., Gonor. & Ven. Dis. **26**:656 (Sept.) 1942.

7. Kast, C. C., and Kolmer, J. A.: A Note on the Cultivation of Treponema Pallidum with the Preservation of Virulence, Am. J. Syph., Gonor. & Ven. Dis. **27**:309 (May) 1943.

practical importance to the syphilologist. Under the dark field microscope this differentiation may be very difficult. Were cultivation and isolation of oral spirochetes a practicable clinical procedure, more clearcut distinctions might be possible. Wichelhausen and Wichelhausen [8] have been able to obtain pure cultures of spirochetes from fusospirochetal oral lesions. The isolation of these strains was accomplished by filtration through Chamberland-Pasteur filters, by cultivation in deep agar shake tubes and by anaerobic cultivation in the depth of blood agar plates. The morphologic and cultural characteristics of nineteen strains of oral spirochetes are described. Two of these strains were serologically related to each other and to culture strains of organisms (Reiter, Kazan) originally considered to be S. pallida.

Survival in Frozen Plasma.—The rapid increase in the popularity of blood banks throughout the country and particularly the accumulation of large stores of plasma, liquid, frozen or dried, have made important the study of survival of S. pallida in these various preparations.

Ravitch and Chambers [9] report that human and rabbit plasma heavily inoculated with S. pallida and frozen at — 20 C. for forty-eight hours or longer is not infectious for normal rabbits. Such material was infectious, however, when the freezing period was only twenty-four hours. Under these conditions the incubation period is prolonged even though the experimental animals received an inoculation dose twice the size of that given the controls.

Appearance in the Blood Stream.—The precise time at which S. pallida enters the general circulation after inoculation into man is not known. In experimental animals, the organisms have been demonstrated to enter the blood stream within a relatively few minutes. In man, it is commonly taught that spirochetemia develops just prior to the appearance of the secondary lesions.

Evidence that S. pallida may invade the blood stream before the lesions of early syphilis appear is furnished by Bickers.[10] This author reports a case of congenital syphilis in a newly born child acquired before the appearance of the primary sore in the mother. The mother was known to have negative serologic reactions for syphilis ten months, one month and two weeks before the chancre developed, and a history of contact with an infected partner twenty-two days before the lesion appeared was established. The chancre became obvious three days post partum and was followed five weeks later by a secondary eruption. At the age of 3 weeks the infant showed lesions of congenital syphilis and had a positive serologic reaction of the blood.

Treatment-Resistant Strains of S. Pallida.—Further studies on a treatment-resistant strain of S. pallida have been reported by Beerman and Severac.[11] When a patient with syphilis fails to respond to the usual antisyphilitic therapy, it is considered that the resistance is due to one or a combination of the following factors: the peculiarities of the host; the potency of the antisyphilitic remedy, and a special biologic peculiarity of the strain of S. pallida.

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8. Wichelhausen, O. W., and Wichelhausen, R. H.: Cultivation and Isolation of Mouth Spirochetes, J. Dent. Research **21**:543 (Dec.) 1942.

9. Ravitch, M. M., and Chambers, J. W.: Spirochetal Survival in Frozen Plasma, Bull. Johns Hopkins Hosp. **71**:299 (Nov.) 1942.

10. Bickers, W.: Congenital Syphilis Acquired by Fetus Before Appearance of Chancre in Mother, Arch. Dermat. & Syph. **46**:135 (July) 1942.

11. Beerman, H., and Severac, M.: The Problem of Treatment-Resistant Syphilis: Further Studies on a Treatment-Resistant Strain of Spirocheta Pallida, J. Invest. Dermat. **5**:269 (Oct.) 1942.

The opportunity for the present study was afforded by a patient with early syphilis whose early lesions failed to respond to a total of 5.4 Gm. of various arsenicals but did respond to prolonged use of a bismuth compound intramuscularly and nonspecific therapy. The problems considered were, first, the characteristics of the strain of S. pallida isolated from this treatment-resistant patient, and second, the comparative effect of arsphenamine treatment on rabbits infected with this strain as compared with rabbits infected with the Nichols-Hough strain.

As the strain studied was carried through successive transfers, it appeared to acquire enhanced virulence for rabbits. At first, the percentage of "takes" was low, the incubation period variable and the lesions atypical. Later, inoculation resulted in characteristic manifestations after a standard period of incubation in a high percentage of animals. Experiments to determine the response to treatment were controlled by the use of the Nichols-Hough strain of organisms and by the use of a standard lot of arsphenamine, the minimal sterilizing dose of which over more than ten years had been 14 mg. per kilogram of body weight. Thirteen of 51 rabbits infected with the treatment-resistant strain were not sterilized by injection of from 14 to 30 mg. per kilogram of body weight. This refractoriness to treatment was sporadic, more pronounced in the beginning of the study, and less frequent as the strain became adapted to the new host. The study indicates that there is no regularity in the occurrence of refractoriness to treatment in rabbit syphilis, despite suggestive chains of instances of such resistance.

EXPERIMENTAL SYPHILIS

Syphilitic Women as Passive Carriers.—As a factor in the spread of syphilitic infection, the sexually promiscuous woman with latent or treated syphilis long has been considered to play an important role as a passive carrier. Pariser [12] has subjected this preconceived belief to experimental study.

In his three experiments, S. pallida was introduced into the vaginas of women with early syphilis. Subsequently, a search for the organism was made by dark field microscopic examination and by inoculation of rabbits intratesticularly. Spirochetes thus introduced into the human vagina survived only a relatively short time. In one instance organisms were recognizable morphologically in the vagina until four hours after they were introduced, and in another they disappeared within one and a half hours, after which time the infectiousness of the vaginal secretions could not be demonstrated by animal inoculation.

Infectiousness of Seminal Fluid.—In a study of the infectiousness of the semen of men with early syphilis, Pariser [13] found that seminal fluid did not transmit the disease to susceptible animals except when it was contaminated with S. pallida while passing over an open lesion containing the organisms. In his study, 23 specimens of seminal fluid from 20 men with early syphilis were used. Two experimental methods were employed. Ten specimens of seminal fluid were injected into the dorsal skin of mice; the peripheral lymph nodes, the spleen and in some instances the brain were removed twenty-one to forty days later; the macerated organs were suspended in saline solution and injected intratesticularly into rabbits. The remaining 13 specimens were injected directly into the testes of rabbits. Dark field examinations were made on all freshly passed seminal fluid specimens, but no spirochetes

12. Pariser, H.: Studies of the Transmissibility of Syphilis: The Role of the Syphilitic Woman as a Passive Carrier, J. Invest. Dermat. **5**:243 (Oct.) 1942.

13. Pariser, H.: Studies of the Transmissibility of Syphilis: The Infectiousness of the Seminal Fluid of Men with Early Syphilis, J. Invest. Dermat. **5**:311 (Dec.) 1942.

were seen in any of the specimens. The results of animal inoculation were also negative, except in 1 case in which the patient had moist papular lesions near the meatus and extending into the canal.

The author postulates that the male can transmit syphilis only during the presence of open lesions containing S. pallida, whether chronologically early or late in the course of the infection.

Time Factor in Evaluation of "Cure" of Rabbit Syphilis.—The finding that the lymph nodes of untreated syphilitic rabbits remain infectious for years, often in the absence of other demonstrable evidence of syphilis, has led many investigators to depend on the results of lymph node transfers as the ultimate criterion of cure in the experimental disease.

Eagle, Hogan and Kemp [14] enjoin caution in the interpretation of such negative lymph node transfers. They have found the time at which the transfer is made to be an important factor. Of 546 syphilitic rabbits treated with various arsenical drugs in doses approximately 25 to 75 per cent of the amount judged to be curative, 394 apparently were "cured" as judged by negative lymph node transfers into normal rabbits *six weeks* after treatment. However, when 279 of these "cured" animals were retested by a second node transfer *six months* after treatment, no less than 10 (37 per cent) were found still to harbor the organisms. The authors interpret these negative lymph node transfers followed by positive transfers as analogous to early infectious relapse in man.

Existing data as to the curative dosage of various antisyphilitic drugs must be reconsidered with attention to the time at which node transfers were made. Until that factor is rigidly controlled, temporary "cures" constitute a variable and indeterminable error which may vitiate the significance of much experimental data.

Criteria of "Cure" of Rabbit Syphilis.—The evaluation of chemotherapeutic preparations depends on their effectiveness in ridding experimental animals of the invading organisms. It is difficult to be sure that an animal has been sterilized of spirochetes, and the criteria of "cure" are not universally agreed on.

Worms,[15] in a review of the subject, points out that, although recent workers appear to accept the validity of lymph node transfer as a safe procedure for the evaluation of antisyphilitic drugs, there is experimental evidence to indicate that success with this procedure is not entirely acceptable as a criterion of cure. This evidence is: (1) the occurrence of "nullers," animals which acquire symptomless infection when inoculated with lymph node suspensions; (2) variability in the dissemination of the organisms throughout the organs of the body. Factors involved include the stage of the infection at which treatment is started and the interval of time between treatment and test of cure.

In testing the effectiveness of a chemotherapeutic preparation, Worms suggests:

(1) The preparation under examination should be tried finally not only on syphilitic rabbits but also on syphilitic mice. In rabbits it should be tried in the latent stage after the first outbreak of active symptoms, i. e., about three to four months after infection, and in mice not less than two months after the inoculation, when the infection of the central nervous system has been well established.

(2) The test by tissue transfer should be performed in rabbits not less than one year after the treatment, and during the year the rabbits should be closely watched for any signs of recurrence. In mice the test should be made in not less than six to eight months after treatment.

14. Eagle, H.; Hogan, R. B., and Kemp, J. E.: The Importance of the Time Factor in the Evaluation of "Cure" in Syphilitic Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **26**:557 (Sept.) 1942.

15. Worms, W.: Evidence of Cure in Experimental Syphilis When Used for the Evaluation of Chemotherapeutic Preparations, Brit. J. Ven. Dis. **19**:15 (March) 1943.

(3) For the transfer the material should be used as follows: (a) Emulsions of a mixture of spleen, liver, marrow of several bones and testes of the treated rabbits; (b) emulsion of several lmph glands of the treated rabbit; (c) emulsion of whole organs (including brain, which should be transferred separately) and of several lymph glands of the treated mouse.

Rabbit tissue emulsions should be inoculated into other animals, and if no signs of infection become apparent a second passage should be made. To quote Worms further:

Admittedly this is all troublesome but it is only by such thoroughness in testing that the inherent fallacies in the transfer method can be minimized; the trouble, time and expense are justified when a judgment of the value of a chemotherapeutic preparation depends on the result.

Experimental Primary Atrophy of the Optic Nerve.—Longley, Clausen and Tatum [16] have experimentally produced primary atrophy of the optic nerve in monkeys by the administration of various pentavalent arsenical compounds, including sodium arsanilate, tryparsamide, acetarsone, 3-amino-4-betahydroxyethoxyphenylarsonic acid and 4-β-(β' hydroxy)-ethoxyethoxyphenylarsonic acid. The "approximate blinding dose" of acetarsone was found to be about three times, and of tryparsamide nearly nine times, that of sodium arsanilate. Of interest is the fact that 4-β-(β'-hydroxy)-ethoxyethoxyphenylarsonic acid, a compound which contains no amino group, produced characteristic visual damage in one of three animals tested. The toxicity of the drug thus appears to be a function neither of the position of a nitrogen-containing side chain nor of its presence.

This work makes available an experimental basis for study of the toxicity (blinding potentialities) of arsenical compounds and for evaluation of the prophylactic procedures designed to reduce or eliminate toxic optic neuropathy resulting from chemotherapy of syphilis of the central nervous system.

McDermott and his co-workers [17] point out that the mechanism of the production of tryparsamide amblyopia has always been obscure. They review the literature pertaining to the development of amblyopia following vitamin deficiency. The B complex and vitamin A have both been incriminated. It is difficult to determine the exact dietary factor concerned in the various clinical observations, since the deficiency is almost always a multiple one. Likewise, the results in experimental animals are also not free from conflict, but it has been established that proper utilization of at least two dietary factors is necessary for the maintenance of the integrity of the nervous system in animals. These two essential substances are vitamin A and some fraction or fractions of the B complex which is not thiamine, riboflavin or nicotinic acid.

In the present experiment, young growing rats of both sexes were put on diets deficient in vitamin A and the B complex. The authors summarize the experiment as follows:

1. Deficiencies of vitamin A and of several components of the B complex were produced in rats. Certain groups of these deficient animals as well as normal rats were treated with tryparsamide.

2. Rats maintained on synthetic diets lacking only the complete vitamin B complex showed degeneration of the optic nerve. This degeneration was intensified by the concurrent administration of tryparsamide.

16. Longley, B. J.; Clausen, N. M., and Tatum, A. L.: The Experimental Production of Primary Optic Atrophy in Monkeys by Administration of Organic Arsenical Compounds, J. Pharmacol. & Exper. Therap. **76**:202 (Nov.) 1942.

17. McDermott, W.; Webster, B.; Baker, R.; Lockhart, J., and Tompsett, R.: Nutritional Degeneration of the Optic Nerve in Rats: Its Relation to Tryparsamide Amblyopia, J. Pharmacol. & Exper. Therap. **77**:24 (Jan.) 1943.

3. Rats maintained on the same synthetic diet supplemented either with brewer's yeast or with all the available crystalline B-vitamins together (thiamine hydrochloride, riboflavin, nicotinic acid, pyridoxine, calcium pantothenate and choline chloride) showed no degeneration of the optic nerve, whether or not they had received tryparsamide.

4. Rats maintained on diets which were partially deficient in pantothenic acid failed to show any degeneration of the optic nerves, whether or not they had received tryparsamide.

5. The deficiency responsible for the nerve degeneration in completely B-deficient rats is attributable to one or more of the known crystalline members of the group. It is not pantothenic acid alone.

6. Rats maintained on synthetic diets completely free of vitamin A developed marked degeneration of the optic nerves.

7. There was no evidence that the administration of tryparsamide intensified this process. The changes in the tryparsamide treated animals were, if anything, somewhat less than in the untreated animals, but this effect is probably only an apparent one as the changes were extensive in both groups.

8. Rats maintained on diets poor in vitamin A which were treated with tryparsamide, showed degenerative changes in the optic nerves although they showed no clinical signs of A deficiency.

9. The degenerative changes in the low vitamin A group were of much less extent than in the completely deficient animals, either treated or untreated.

10. Rats maintained on synthetic diets supplemented by adequate amounts of B-complex (yeast) and vitamin A (cod liver oil) developed no degeneration of the optic nerve, whether or not they were treated with tryparsamide.

SYPHILOID DISEASES

Pinta.—An extensive review of the literature relating to pinta has been made by Holcomb,[18] who cites 177 references. Pinta has been reported in the southern states of Mexico, Colombia, Venezuela, Brazil, Ecuador, Peru and the West Indies, where it affects principally Negroes, native Indians and peoples of mixed blood. Descriptions of the disease are not limited to the Western Hemisphere, however, for cases have occurred on the east and west coasts of Africa, in Egypt, Tunisia, Algeria, Morocco and Iraq, and among the dark-skinned races in India, Straits Settlement and the Philippine Islands.

The etiologic agent, a spirochete morphologically indistinguishable from S. pallida and Treponema pertenue, was first identified by two Cuban physicians, Grau Triana and Alfonso Armenteros. It has been named variously Treponema carateum, Treponema herrejoni, Treponema pictor, Treponema americana, Treponema discromoderma, and Treponema pintae. A limited number of inoculations into guinea pigs, rabbits and rats have given negative results. Serologic tests for syphilis are usually positive, especially after the disease becomes chronic.

Several insects have been found to harbor the spirochete of pinta and are thought by some to be vectors of the disease. Others believe personal contact to be more important, pointing out that the organism can be demonstrated in the perspiration of infected persons.

In tracing the antiquity of literature on hyperpigmentation and depigmentation, Holcomb discusses the question of whether pinta originated in the Western Hemisphere or was imported from Africa. He also indicates certain relationships to yaws and syphilis, concluding that: "A review of the literature would seem to me to indicate that this syphiloid is one of the many disguised evidences of the antiquity of syphilis."

Beerman[19] defines pinta (mal del pinto, carate, azul) as:

18. Holcomb, R. C.: Pinta; A Treponematosis, U. S. Nav. M. Bull. **40**:517 (July) 1942.
19. Beerman, H.: Pinta—A Review of Recent Etiologic and Clinical Studies, Am. J. M. Sc. **205**:611 (April) 1943.

. . . a chronic endemic disease of long duration, infectious, possibly contagious or transmissible by an as yet unknown vector. It is characterized by papular or papule-like initial lesions and is followed in a variable but usually long time by an erythematosquamous eruption which increases continuously and is transformed into dermatitic plaques which are superficial, atrophic, pigmented and achromic, accompanied frequently by palmar or plantar keratodermias, and enlargement of superficial lymph nodes. It is now supposed to be due to a specific treponema. The cutaneous lesions are at times accompanied by visceral changes (aorta, nervous system).

Pinta affects dark-skinned peoples chiefly. It is essentially a disease of rural communities and is most prevalent in river valleys. Persons of the poorer classes, laborers and persons living under unsanitary conditions most often are affected. It occurs mostly between the ages of 10 and 20 years. The mode of transmission is thought to be direct contact, intimate and prolonged, but the possibility of an insect vector exists.

Serologic tests of the blood for syphilis, both complement fixation and flocculation, give uniformly high percentages of positive reactions, especially during the later stages of the disease. The treatment of pinta is similar to that of syphilis and of yaws. Seroresistance is the rule rather than the exception. As Beerman says:

Pinta thus represents another milestone in the efforts to evaluate the syphilis-like diseases. . . . With the discovery of an organism, morphologically indistinguishable from *Spirochaeta pallida*, the laws of Koch have been fulfilled only a little less than in syphilis. But with this discovery of the treponemal cause of pinta, comes rationalization of effective therapy previously used empirically. With increased knowledge of the clinical aspects of the disease and the possible modes of its transmission, prophylaxis can be successfully employed. Credit is due to the indefatigable industry of the workers in our neighboring Latin American countries.

In Venezuela, according to Iriarte,[20] pinta is found mostly in the western states and in the extreme south. Studies purporting to establish a mycologic causation are considered untenable, since many of the fungi described are saprophytic on the skin of animals and man. T. carateum, while found readily in the dyschromic cutaneous lesions, has not been demonstrated in the lymph nodes of patients with pinta.

SERODIAGNOSIS OF SYPHILIS

Spirochetal Antigens.—There is reason to believe that an antigen made from pure cultures of pathogenic S. pallida would be more specific than the tissue antigens now used in the serologic laboratory. The difficulty is, of course, in obtaining pure cultures or organisms which retain their pathogenicity.

Sordelli [21] summarized the various attempts which have been made to utilize spirochetal antigens in serodiagnosis. Although no original work is presented, this article provides a splendid summary of the subject. The relationship between reagin and immunity, the cross reactions between various strains of pathogenic and cultivated spirochetes and the results obtained with human serums with various spirochetal antigens are all described. To date, the hope that biologic false positive reactions can be excluded by using these antigens has not been realized. In yaws and pinta, results are similar to those obtained with tissue antigens; in malaria, positive reactions are common, but in leprosy the proportion of falsely positive reactions is less than with standard tests.

Antigens: Flagellar and Somatic.—The fact that antiserums to somatic type antigens lose their flocculating power with less heating than do antiserums to flagellar type antigens generally has been accepted as evidence that antibodies to

20. Iriarte, D. R.: En carate en Venezuela, Rev. de med. trop. y parasitol., bacteriol., clin. y lab. **8**:75 (Nov.-Dec.) 1942.

21. Sordelli, A.: Las espiroquetas como antigeno, Rev. argent. dermatosif. **26**:777, 1942.

the two kinds of antigen differ in their resistance to heat. Bawden and Kleczkowski [22] report experiments to show that this different reactivity to heat depends on the presence of albumin. If euglobulin fractions of antiserums were prepared and heated separately, there was no difference in the amount of heating required to destroy the flocculating power of different antibodies. Only when the antibodies to the two types of antigen were heated in the presence of albumin was there any difference in their behavior. When ability to fix complement or to neutralize infectivity was used as a criterion of the presence of residual antibodies, instead of ability to cause flocculation, all antiserums were found to be equally susceptible to heat. The fact remains, however, that heating (to 75 C. for ten minutes) destroys the ability of antiserum to somatic type antigens to cause flocculation, although not its ability to combine with the antigens.

In view of the known differences, e. g., the thermolability of various antibodies, attempts to differentiate true syphilitic reagin from nonspecific substances (antibodies?) of nonsyphilitic serums continue to offer some promise. Kahn's several "verification" tests represent efforts in this direction, even if their consistency and specificity are yet to be proved.

Natural Tissue Antibody.—Kidd and Friedewald [23] described experiments which demonstrate the presence of a natural antibody in the blood of normal adult rabbits which reacts in vitro with a sedimentable constituent of normal rabbit tissue cells. The substance with which the natural tissue antibody reacts is regularly present in saline extracts of many normal tissues. The titer of this principle was found to run parallel with that of two natural antibodies also present in normal rabbit's blood (natural Wassermann reagin and natural anti-sheep hemolysin), but absorption tests showed it to be distinct from these.

The natural tissue antibody apparently fails to react in vivo with normal tissue substance. In this respect, it is comparable to Wassermann reagin, since although the tissues of syphilitic patients contain antigenic substances and antibody to this substance is present in the blood serum, no demonstrable reaction occurs in vivo.

Zone Reactions.—As with other serologic procedures, such as the Widal test for typhoid, so also with serologic tests for syphilis there is occasionally observed a prezone phenomenon responsible for false negative reactions of serums which should give a strongly positive reaction. With such serums it is necessary to test serial dilutions to bring out the positive reaction.

Myers and Perry,[24] testing serums from 2,052 patients whose reactions to routine flocculation tests (Kline exclusion) were negative, found 6 showing the prezone phenomenon. In addition to those specimens which gave a negative reaction to the original flocculation test, there were 29 other specimens with atypical doubtful reactions which were really prezone positive reactions. The authors also comment on "an anomalous zone reaction in sera from presumably nonsyphilitic individuals" which they observed 84 times in their study. Unfortunately the clinical status of these patients was not determined. Myers and Perry consider it advisable to use two tests on each specimen of serum, and when it is

22. Bawden, F. C., and Kleczkowski, A.: The Antigenicity of Non-Precipitating Complexes, Brit. J. Exper. Path. **23**:169 (Aug.) 1942; The Effects of Heat on the Serologic Reactions of Antisera, ibid. **23**:178 (Aug.) 1942.

23. Kidd, J. G., and Friedewald, W. F.: A Natural Antibody That Reacts in Vitro with a Sedimentable Constituent of Normal Tissue Cells: I. Demonstration of the Phenomenon; II. Specificity of the Phenomenon; General Discussion, J. Exper. Med. **76**:543 (Dec.) 1942.

24. Myers, R. M., and Perry, C. A.: The Occurrence of Zone Reactions in Flocculation Tests for Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:494 (July) 1942.

not feasible to perform more than one test they recommend that at least two different quantities of serum be used routinely.

Antibody Formation and the Anamnestic Reaction.—In a review of the general problem of antibody production and the anamnestic reaction (the phenomenon of antibody "recall" under the stimulus of specific and nonspecific antigens), Cannon [25] states:

> The anamnestic reaction may . . . play a beneficial role in the treatment of chronic or focal infections in which, presumably, foci of infective agents persist in the tissues over long periods of time. For example, in the treatment of chronic syphilis, arthritis, or iritis, stimulation of the antibody mechanism by various foreign protein materials, such as typhoid vaccine, milk, malarial parasites, or by hyperthermic means may cause the liberation into the blood stream of significant amounts of specific antibodies engendered by previous antigenic experiences but which could not otherwise gain access to the infected foci.
>
> The facts . . . suggest that antigenic components may persist within antibody-producing cells for considerable periods of time after infection or vaccination and thus are able to function as 'templates' when later stimuli cause an acceleration of antibody production.
>
> Whenever (antibody) is formed, antigenic 'templates' may . . . so influence the structural pattern of the globulin molecules as to confer specific properties upon them. Some of these molecules may pass into the extracellular fluids as antibodies and remain there for variable periods of time; others may persist within their cells of formation. The persistence of this antibody matrix for months or years may explain both the acquisition of acquired resistance independently of any considerable amounts of antibodies in the blood as well as many of the tissue reactivities which are commonly regarded as allergic phenomena.

Absence of Reagin from Urine.—Shortly after the discovery of complement fixation and its application to the serodiagnosis of syphilis, several investigators reported the presence of a complement-fixing substance in the urine of patients with syphilis. Other workers, finding urine anticomplementary, were unable to confirm this finding.

Scott,[26] who has tested the urine of 23 patients with syphilis and of 8 nonsyphilitic controls, reports that in no instance was reagin demonstrable by complement fixation. Five patients with syphilis had albuminuria, 1, a patient with early syphilitic nephrosis, excreting 2.0 Gm. of albumin per liter. None of the specimens of urine, however, contained reagin, despite the fact that the blood reagin titers ranged between 24 and 48 units. Urine frequently was found to be anticomplementary despite neutralization. This anticomplementary activity seemed directly proportional to the volume of urine.

The author concedes that an occasional patient may excrete reagin in the urine. For this to occur, two factors appear necessary: first, a relatively high percentage of globulin in the excreted protein, which presupposes severe damage to the glomerular filter; second, a high reagin content in the blood serum. Neither of these factors existed in sufficient degree in the patients of the group here studied.

Weltman's Serum Coagulation Reaction in Syphilis.—When normal human serum is diluted 1:50 with differently concentrated solutions of calcium chloride in distilled water, different intensities of turbidity and flocculation occur after fifteen minutes of heating. In certain diseases the serum coagulation becomes altered, and it has been claimed that by determining the concentration "band" at which coagulation occurs it is possible to differentiate "exudative" from "fibrotic" conditions.

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25. Cannon, P. R.: Antibody Production and the Anamnestic Reaction, J. Lab. & Clin. Med. **28**:127 (Nov.) 1942.

26. Scott, V.: Note on Absence of Syphilitic Reagin and Antigenic Substance in Urine, Bull. Johns Hopkins Hosp. **71**:242 (Oct.) 1942.

Steiner,[27] who has studied the serum coagulation reaction in a group of 72 syphilitic patients, reports that in general the coagulation bands tended toward moderate but distinct prolongation, although in most instances they were not specific alterations. No distinct differentiation among the various stages or manifestations of syphilis was possible. No relation was present between the coagulation reaction and the Wassermann reaction.

Colloidal Gold Reaction.—It has been impossible heretofore to study the effects of the individual globulin fractions on colloidal gold precipitation, because these fractions could not be obtained in pure form. Gray,[28] using pure protein fractions prepared electrophoretically, has studied the effects on the colloidal gold flocculation of pure human albumin, gamma globulin and the fraction containing alpha and beta globulins.

The addition of pure gamma globulin to normal spinal fluid produced a dementia paralytica type colloidal gold curve. The degree of flocculation was proportional to the amount of gamma globulin added. Similar concentrations of the fraction containing alpha and beta globulin did not affect the colloidal flocculation. The addition of pure human albumin to cerebrospinal fluid of a patient with dementia paralytica converted the curve to normal. Since the gamma globulin is increased in the spinal fluid of patients with dementia paralytica, the colloidal curve typical of that disease probably depends on the relative increase in gamma globulin.

Studying the protein components of cerebrospinal fluid with the Tiselius electrophoresis cell, Kabat, Moore and Landow [29] found that the electrophoretic pattern of spinal fluid resembles that of serum and that alterations in the composition of the serum proteins are reflected in the spinal fluid. In neurosyphilis, an increased gamma globulin occurred in the cerebrospinal fluid. No such change was found in the blood serum. This suggests that not all of the spinal fluid protein is derived from the blood, since it is difficult to imagine an altered permeability of the hematoencephalic barrier which could produce an increase in gamma globulin without producing an increase in the smaller albumin molecule.

Colloidal gold activity of the cerebrospinal fluid was found to be associated with increases in the gamma globulin fraction, whereas albumin appeared to inhibit this reaction.

FALSE POSITIVE REACTIONS TO SEROLOGIC TESTS

Summarizing the present status of biologic false positive serologic reactions for syphilis, Eagle [30] outlines the procedures which have been suggested for differentiating syphilitic reactions from those due to other conditions.

Two of the suggested procedures are the differential temperature "verification" test of Kahn, which "is not yet a test on which to base a definite opinion as to the significance of a positive result," and the spirochetal complement fixation test, the results of which are "so completely at variance . . . that it is well to withhold judgment." To quote further:

> Fundamental studies on the nature of the substance responsible for these biologic false reactions are clearly indicated. At the onset, it may be advisable to distinguish between four

27. Steiner, K.: Weltman's Serum Coagulation Reaction in Cases of Dermatoses and of Syphilis, Arch. Dermat. & Syph. **46**:87 (July) 1942.

28. Gray, S. J.: Studies on the Mechanism of the Spinal Fluid Colloidal Gold Reaction, Proc. Soc. Exper. Biol. & Med. **51**:401 (Dec.) 1942.

29. Kabat, E. A.; Moore, D. H., and Landow, H.: An Electrophoretic Study of the Protein Components in Cerebrospinal Fluid and Their Relationship to the Serum Proteins, J. Clin. Investigation **21**:571 (Sept.) 1942.

30. Eagle, H.: Biologic False Positive Serologic Tests for Syphilis, editorial, Am. J. Syph., Gonor. & Ven. Dis. **26**:641 (Sept.) 1942.

types of reagin, some of which may ultimately prove to be identical: (a) The flocculating factor present in minute traces in many normal human sera; (b) the 'reagin' present in the occasional human serum in amounts sufficient to give positive or doubtful diagnostic tests; (c) the 'reagin' elaborated in the course of such nonsyphilitic diseases as leprosy, malaria, cowpox, and infectious mononucleosis, to mention only a few; and finally, (d) the 'reagin' elaborated in the course of syphilitic infection. . . .

Corollary to the possible chemical identification of the serum components responsible for the several types of reactivity, studies should be carried out on the fractionation of crude tissue extracts used as 'antigen' in the Wassermann and flocculation tests; for it is possible that the different types of 'reagin' react with different substances in those extracts.

False Positive Reactions Following Routine Immunizations.—Alterations in the blood serum brought about by routine United States Army immunizing procedures against various diseases (smallpox, typhoid, yellow fever and tetanus) have been shown by Arthur and Hale [31] to influence the results of the Kahn flocculation test for syphilis. Serologic tests were performed on 94 recruits who had received routine Army preventive inoculations. Of those studied, 14 (14.8 per cent) were found to have temporarily positive Kahn reactions. This change persisted for one or two months and then disappeared. It is not possible to determine from the data given whether the falsely positive serologic reactions resulted from any one of the inoculations or from the combination of all four.

Because of the extensive use of serologic tests for syphilis among military service personnel who may have received preventive inoculations shortly before, the observation that temporarily falsely positive reactions for syphilis may result from these inoculations is a timely contribution to the serodiagnosis of syphilis.

False Positive Reactions Following Smallpox Vaccination.—Favorite [32] has confirmed the observation that smallpox vaccination may cause a falsely positive serologic reaction for syphilis. A group of 202 medical students and nurses known to have negative serologic reactions were vaccinated and repeatedly tested with Kolmer, Kahn and Mazzini tests. Twenty-four persons (11.8 per cent) had positive reactions at one time or another following the vaccination. The patients with positive reactions were retested every two weeks. There was a gradual diminution in the intensity of the reactions until all became negative by the end of one hundred and twenty days.

Lubitz [33] considers smallpox vaccination an important cause of biologic false positive serologic reactions for syphilis. He has performed serologic tests on 100 persons whose vaccination resulted in primary "takes." Of these, 13 gave positive reactions. There was no consistent evidence of heterophile antibody formation, and the Kahn verification test gave no conclusive indication that these were false positive reactions.

Specificity of Serologic Reactions During Pregnancy.—In the earlier literature on serodiagnosis, the belief frequently was expressed that during pregnancy serologic tests for syphilis were unreliable. That this belief is entirely false is again substantiated by the data of Kandler.[34] Several different technics were used in the study of 10,354 pregnant women, and no evidence was found that either the sensitivity or the specificity of the serologic procedures was impaired.

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31. Arthur, R. D., and Hale, J. M.: Biologic False Positive Tests for Syphilis Associated with Routine Army Immunizations, Mil. Surgeon **92**:53 (Jan.) 1943.

32. Favorite, G. O.: Effects of Smallpox Vaccination (Vaccinia) on Serologic Tests for Syphilis, Proc. Soc. Exper. Biol. & Med. **54**:297 (April) 1943.

33. Lubitz, J. M.: Serologic Reactions Following Smallpox Vaccination, Proc. Inst. Med. Chicago **14**:343 (Feb.) 1943.

34. Kandler, H.: Ueber die Zuverlassigkeit der Seroreaktionen auf Syphilis bei Reihenuntersuchungen von Schwangeren, Arch. f. Dermat. u. Syph. **181**:315, 1940.

False Positive Reactions in Infants and Children.—Surveying the results of approximately 26,700 flocculation tests for syphilis made in pediatric service, Hill [35] found 114 tests made on 37 patients which elicited proved false positive or false doubtful reactions. A major portion of the nonspecific reactions noted in the study occurred in patients with infections of the respiratory tract in particular and acute infections in general, but occasional false doubtful and false positive reactions occurred with a variety of other conditions.

Serologic Reaction Approaching "Universal Sensitivity."—Kahn and his co-workers [36] have studied the extent to which it is possible to increase the number of false positive reactions given by a serodiagnostic test by increasing the sensitivity of the test. The use of excessively sensitive antigens gave as high as 40 per cent false positive reactions. The use of such antigens with the test performed at 1 C. resulted in about 80 per cent false positive reactions. When, in addition, unheated serums were used (rather than serums heated for thirty minutes at 56 C.), the nonspecific sensitivity approached 100 per cent. These findings suggest to the authors the existence of a universal serologic reaction which may afford the basis for false positive reactions obtained with serodiagnostic tests.

"Verification" Tests.—A new method purporting to "verify" the results of questionable serologic tests for syphilis is described by Kahn.[37] This new procedure is based on the effect of different concentrations of electrolytes on the flocculation reaction.

A higher titer on serial dilution with 2.5 per cent solution of sodium chloride than with 0.9 per cent concentration denotes, according to the author, a "syphilitic type" of reaction, whereas a higher titer on serial dilution with 0.9 per cent salt solution than with 2.5 per cent concentration denotes a "general biologic (non-syphilitic) type" of reaction.

This new "verification" procedure has not yet been applied to any large series of cases, and its ultimate place in the serodiagnosis of syphilis, therefore, awaits further study. Its precursor, based on variations in reactivity at different temperatures, has not been widely accepted.

Carter [38] believes the differential temperature "verification" test procedure can be improved by the use of parallel quantitative reactions run at temperatures 37 and 1 C., thus furnishing a contrasting relationship of the strength of the reactions of a serum at the two temperatures.

Briceño Rossi [39] has attempted to distinguish serum reagin due to syphilis from that due to yaws and pinta by using Kahn's differential temperature "verification" test. In general, the serums of patients with yaws or pinta gave the "syphilitic" type of reaction rather than the "general biologic" type. Serums from 30 lepers were also tested: 19 gave negative reactions; 4 gave equally positive reactions at 37 and at 1 C.; 3 gave the "syphilitic" type reaction and 4 the "general biologic" type.

35. Hill, A.: Nonspecific Serologic Reactions for Syphilis in Infants and Children, J. Pediat. **21**:207 (Aug.) 1942.

36. Kahn, R. L.; Marcus, S.; McDermott, E. B., and Adler, J.: Serologic (Nonsyphilitic) Reaction Approaching Universal Sensitivity, J. Invest. Dermat. **5**:459 (Dec.) 1942.

37. Kahn, R.: A New Verification Method in Serology of Syphilis: A Preliminary Report, Univ. Hosp. Bull., Ann Arbor **8**:45 (June) 1942.

38. Carter, B. B.: The Use of a Quantitative Test in Verification Procedures, Am. J. Syph., Gonor. & Ven. Dis. **26**:629 (Sept.) 1942.

39. Briceño Rossi, A. L.: El valor del verifications test, en la serologia del carate o mal del pinto y buba (pian o yaw), Rev. san. y asist. Soc. **8**:153 (Feb.) 1943.

False Negative Serologic Reactions.—Many recent publications have stressed the importance of false positive serologic reactions for syphilis. Souders [40] properly notes that there may be false negative reactions as well. Serum from a syphilitic patient with active manifestations of the disease may give a negative reaction from laboratory error, because of low sensitivity of the test used, when the infection had existed for many years and if therapy had been employed. Other causes not mentioned by Souders include the occurrence of a zone phenomenon and the occasional finding of a person whose response to syphilitic infection does not include the elaboration of reagin.

PREVALENCE OF SYPHILIS

The Problem of Measurement.—Inherent in any program to control syphilis is the problem of measuring the frequency of the disease and its trend in relation to that program over a period of years. Attempts at measurement in the past have not been generally satisfactory, either because the data on which they were based were not reliable or because the significance of those data was not properly interpreted.

Turner [41] discusses some of the underlying principles of the measurement of syphilis. He points out that in the measurement of the frequency of the disease, data related to *incidence* (the rate at which persons are being infected) must be differentiated from data related to *prevalence* (the accumulation of affected persons in the community).

Factors other than the actual frequency of syphilis may cause variations in the crude incidence and prevalence rates. Moreover, changes in the group under study may result in variations in the frequency of syphilis quite independent of the operation of control measures. Unless correction is made for these variables, data for one year may not be comparable with those of another. The principal variable factors are those related to the individual patient (variable criteria for the diagnosis of syphilis, variation in sensitivity and specificity of serologic tests) and those related to the group being studied (race, sex, age, social and economic factors, selection of patients included in the study group).

The author reviews recent studies on the incidence and prevalence of syphilis in the United States, concluding that most are so weighted with selective factors of one sort or another that direct comparisons from year to year to determine the trend of the disease cannot be made.

Discovery Rates.—Each year in a given community a certain number of cases of syphilis are discovered medically for the first time. When the number of these newly discovered cases is related to the population of the community, discovery rates may be derived, and these rates may be used as one index of the trend of the disease within the community.

A discussion of the reliability and significance of such discovery rates obtained from the study of an urban area over a nine year period from 1932 to 1940 inclusive has been given by Turner and his co-workers.[42]

In the Eastern Health District of Baltimore, the mean annual discovery rate for all cases among Negroes was 26.7 per thousand of population and among white

40. Souders, C. R.: The Importance of False Negative Blood Tests for Syphilis, Lahey Clin. Bull. **3**:27 (July) 1942.

41. Turner, T. B.: Studies on Syphilis in the Eastern Health District of Baltimore City: I. Principles Concerned in Measuring the Frequency of the Disease, Am. J. Hyg. **37**:259 (May) 1943.

42. Turner, T. B.; Dyar, R.; Clark, E. G., and Birkhead, M. F.: Studies on Syphilis in the Eastern Health District of Baltimore City: II. Discovery Rates as an Index of Trend, Am. J. Hyg. **37**:273 (May) 1943.

persons 1.41 per thousand. Among white persons the mean age-specific discovery rate was highest for the age group 25 to 34 years. Among the Negroes the highest rate was in the 20 to 24 year group. Among both racial groups, the age-specific discovery rates for females were higher than those for males in the younger age group and lower after 25 years. For all ages, the rate for white females was slightly lower than that for males; but among Negroes, there was not any significant difference between the total rates for males and females. In general, Negroes tended to be infected at an earlier age than white persons, and the females of each race tended to be infected at an earlier age than the males.

With regard to the trend of syphilis in the district, the following conclusions are drawn: (1) A substantial reduction in the occurrence of congenital syphilis was noted during the study period; (2) among white persons a significant decline in the mean annual discovery rate occurred; (3) among Negroes there was no convincing evidence of a downward trend in the disease. Discovery rates for total cases of syphilis and discovery rates for cases of early stages showed an upward trend.

Frequency of Syphilitic Lesions at Autopsy.—A significant contribution to the knowledge of the prevalence and the ultimate outcome of syphilitic infection has been made by Rosahn and Black-Schaffer, who have made an extensive and well planned study to correlate clinical and postmortem observations on 5,300 patients at the New Haven Hospital.

Their first paper,[43] as yet unpublished but summarized in their second, is devoted to a review of the literature on the frequency of the changes attributed to acquired syphilis in autopsies on persons over 20 years of age. It was found that changes attributed to syphilis observed at autopsy by 17 investigators varied from a low incidence of 2.6 per cent to a high of 29.5 per cent, with a combined average of 5.45 per cent among 146,761 adults. Analyzing the discrepancies between the findings of different investigators, the authors conclude that the differences are largely based on variability in the histologic changes considered to be evidences of syphilis.

For their own data, Black-Schaffer and Rosahn[44] reviewed 5,300 postmortem examinations performed at the Yale University School of Medicine, of which 3,907 were on patients aged 20 years or more. Three hundred and eighty of the 3,907 patients (9.7 per cent) had clinical, laboratory or postmortem evidence of syphilis. The punch card code used in the study is described in detail. In their third paper, Rosahn and Black-Schaffer[45] discuss the prevalence of the anatomic changes produced by syphilis in adults. In the group of 380 syphilitic patients were 156 persons with morphologic lesions of syphilis. Of the 224 remaining patients, without lesions at autopsy, about half had never received treatment, and a majority had had the diagnosis made by serologic tests alone. Ninety of the 156 patients with anatomic lesions died primarily as a result of syphilis. In the authors' experience, 3 out of 10 persons with syphilis diagnosed by clinical methods had significant lesions in the tissues, and 1 out of 5 died therefrom.

Syphilitic lesions were from two to four times as frequent in Negroes as in white persons. Nevertheless, the syphiltic Negroes appeared no more likely to

43. Rosahn, P. D., and Black-Schaffer, B.: Studies in Syphilis: I. Review of the Incidence of Syphilis in Autopsies on Adults, Arch. Int. Med. **72**:78, 1943.

44. Black-Schaffer, B., and Rosahn, P. D.: Studies in Syphilis: II. Methods of Analysis of Yale Autopsy Protocols, Including a Code for the Punched Card Study of Syphilis, Yale J. Biol. & Med. **15**:575 (March) 1943.

45. Rosahn, P. D., and Black-Schaffer, B.: Studies in Syphilis: III. Mortality and Morbidity Findings in the Yale Autopsy Series, Yale J. Biol. & Med. **15**:587 (March) 1943.

have demonstrable lesions and had no greater chance of dying from the disease than the white patients. The mean age at death of syphilitic and of nonsyphilitic Negroes was identical, but both of these two groups died at a significantly earlier mean age than white persons of comparable categories. This observation suggests that the shorter life expectancy of Negroes as contrasted to white persons may be due not to the greater frequency of syphilis among Negroes but rather to nonspecific social and economic influences which adversely affect their life span.

Sex appeared to have an influence on resistance to the tissue changes of late syphilis, since syphilitic males with lesions at autopsy constituted 4.7 per cent of the male population, whereas syphilitic females with lesions were only 2.7 per cent of the female population, and 44 per cent of the males had demonstrable lesions, in contrast to 33 per cent of the females.

In white patients, the mere fact of syphilitic infection appeared significantly to reduce longevity, regardless of whether or not tissue lesions resulted.

Prevalence of Syphilis in Selectees.—The Selective Training and Service Act of 1940 requires a routine serologic test for syphilis as part of the general examination of every draftee and volunteer. Copies of the reports are forwarded to the United States Public Health Service. An analysis of 1,895,778 such reports on men of draft age has been made by Vonderlehr and Usilton.[46]

The rate of prevalence of syphilis (based on positive and doubtful reactions to serologic tests) among the selectees examined is 45.3 per thousand. Among Negro selectees, the rate of prevalence is 252.3 per thousand, and among white selectees, 17.4 per thousand. In those localities where rates among Negroes are highest, the rates for white persons are relatively higher than in areas where the rates among Negroes are low.

Analyzed geographically, the highest prevalence rates are found in the Southeastern states; the lowest, in the New England, West North Central and Middle Atlantic states. Among selectees from rural areas, the rate of syphilis prevalence is 43.8 per thousand; for those from urban communities, a somewhat higher rate, 46.1 per thousand, is recorded.

As might be expected, syphilis is more prevalent in the older age groups. For example, white urban dwellers had a rate almost four times higher in the age group 31 to 35 years than in the age group 21 to 25 years. This, of course, does not mean that older men more frequently are exposed to syphilitic infection, but indicates rather that there is an accumulation of unrecognized infections in the older age groups.

The information gained from the routine serologic testing of draftees is of great interest to the epidemiologist, and of practical value in determining where venereal disease control activities should be concentrated. The analysis of these serologic tests is indeed the most accurate information available as to the prevalence of syphilis in this country.

Prevalence of Syphilis Among Negroes.—As Smillie[47] points out, the most extraordinary fact brought out by analysis of the results of serologic tests on selectees is the high prevalence of syphilis in the Negro. In all parts of the United States the rate in Negro men is at least ten times higher than in white men.

The geographic distribution of the disease bears a direct relationship to the distribution of the Negro population of the nation. States with a large population of

46. Vonderlehr, R. A., and Usilton, L. J.: Syphilis Among Men of Draft Age in the United States, J. A. M. A. **120**:1369 (Dec. 26) 1942.

47. Smillie, W. G.: Syphilis in the United States Primarily a Negro Problem, J. A. M. A. **122**:365 (June 5) 1943.

Negroes have the highest syphilis rates. Furthermore, those states having highest syphilis rates in Negroes concomitantly have a higher than average syphilis rate in white men. Thus, the major syphilis problem in the United States at the present time centers in the high prevalence of the disease in the Negro.

Comparisons of syphilis prevalence in the United States and in other nations are not valid unless the data presented are truly comparable. When so interpreted, it becomes clear, says Smillie, that in the white population of the United States there is a syphilis rate that compares favorably with that of any nation in the world.

From the point of view of the public health administrator, the issue is cleancut; he must attack the disease most vigorously where it is most prevalent. Since syphilis is more than ten times as prevalent in Negroes as in white persons, ten times as much emphasis should be placed on control of the disease in the Negro race.

Brumfield, Lade and Feldman [48] discuss the prevalence and trend of syphilis in New York state (exclusive of New York city) based on five years' experience with improved morbidity reports. Over the entire period, 79,991 cases of syphilis were reported, of which 71,001 (89 per cent) were classified as instances of acquired syphilis. Of these cases of acquired syphilis, in only 11 per cent was the disease stated to be in an early stage. Prevalence and attack rates were lower in the females than in the males, but the age distribution was essentially the same for the two sexes.

A progressive decline in the number of cases of early syphilis reported and in prevalence and incidence rates was observed during the five year period of study. The decrease was proportionately greater for younger persons, a significant finding, since in this group there is a preponderance of infectious lesions. Notable also is the observation that the decline was more pronounced in cities of 10,000 population and over, in which greater effort was made to control the disease.

Actuarial Data.—Actuarial data which have been used as an index of prevalence of syphilis are by no means satisfactory. There is a tendency to conceal syphilis as a cause of death. Autopsy studies give no indication of the number of patients who have been "cured," whether spontaneously or as a result of antisyphilitic treatment.

In the years 1917 to 1940 inclusive, the adjusted death rate for syphilis for white policy holders of the Metropolitan Life Insurance Company [49] has shown an average annual decrease of 3.9 per cent and for Negro policy holders an increase of 0.5 per cent per year. The adjusted death rate in the first five years of this period was 14.0 per hundred thousand for white persons and 34.0 for Negroes; in the last five years, 7.0 and 37.3 respectively.

The reviewers cannot, however, refrain from commenting that existing actuarial information concerning syphilis is inaccurate, inadequate and incomplete. To estimate the hazard of death from "syphilis" by lumping together in a single group persons with early and latent syphilis, for whom the prognosis after adequate treatment is exceptionally good, and those with late lesions (especially cardiovascular and neurosyphilitic), for whom the prognosis after any sort of treatment may be exceptionally bad, to fail to consider the adequacy of treatment and to base actuarial opinion on serologic standards which are rapidly becoming obsolete and outmoded

48. Brumfield, W. A.; Lade, J. H., and Feldman, L. L.: The Epidemiology of Syphilis Based upon Five Years Experience in an Intensive Program in New York State, Am. J. Pub. Health **32**:793 (Aug.) 1942.

49. The problem of Syphilis, Statist. Bull. Metrop. Life Insur. Co. **23**:8 (Oct.) 1942.

constitute thoroughly unsound actuarial as well as medical practice, and work a profound injustice on many applicants for life insurance. The entire subject of the actuarial hazard of syphilis is badly in need of review by a joint group of clinicians, serologists, pathologists, actuarial experts and independent statisticians.

Syphilis Among Alien Seamen.—Among alien seamen examined at the New York Quarantine Station, reports Burow,[50] the discovery rate of syphilis began to rise toward the end of 1939, reached a peak in the fall of 1940 and has been maintained at a consistently high level since then, being roughly at three times the prewar level. Since May 1941, the discovery rate for gonorrhea has decreased, probably because of the increasingly large number of foreign vessels that carry and utilize sulfonamide compounds.

EPIDEMIOLOGY

A method of syphilis case finding which has received considerable emphasis in recent years is that of contact investigation, particularly as applied to cases of infectious early syphilis.

McIlhany and Smith [51] stress the importance of concentrating efforts at contact investigation on patients with early syphilis. The disease being more transmissible during the first year of infection, epidemiologic studies are most productive if confined to cases of primary and secondary and early latent syphilis of less than one year's duration.

Writing on the epidemiology of communicable venereal disease, Goodman [52] metaphorically compares contact investigation to individual sharpshooting, and screening procedures to spraying the skies with shot to bring down unmarked birds. The essential steps in contact investigation are listed as: (1) *selection* of the patient to be interviewed; (2) *introduction* to determine the patient's identity; (3) *revelation* of contact information; (4) *confirmation* of the information revealed; (5) *localization* of suspected contacts; (6) *investigation* to determine whether the suspect is infected, and (7) *verification* of the infected contact as the source of infection.

Most published studies relating to contact investigation have dealt with the ultimate success of the procedure in terms of infected persons found per original case. Few attempts have been made to analyze the effectiveness of various types of efforts in achieving the desired end in investigations of this type. Packer, McGinnes and Puffer [53] have sought to determine the efficacy of the various technics applied to contact investigation. In their experience, a home visit in which the contact was interviewed was successful in 81.3 per cent of cases. When the contact was not seen but some one else in the household was interviewed, the percentage of success dropped to 56.0 per cent. Telephone calls to the contact's employer were quite successful (58.3 per cent), and telephone calls to the contact achieved 54.3 per cent success. Letters were less useful, being successful for 47.2 per cent of addresses. A study of the cumulative success of epidemiologic efforts on contacts shows that when success is achieved it usually

50. Burow, F. P.: Fluctuation of Venereal Disease Incidence Among Alien Seamen, Ven. Dis. Inform. **24**:45 (Feb.) 1943.

51. McIlhany, L. W., and Smith, D. C.: Epidemiologic Studies in Syphilis, Virginia M. Monthly **70**:130 (March) 1943.

52. Goodman, H.: Essential Steps for Successful Epidemiology in Syphilis and Other Communicable Venereal Diseases, Am. J. Syph., Gonor. & Ven. Dis. **27**:275 (May) 1943.

53. Packer, H.; McGinnes, G. F., and Puffer, R. R.: A Field Study of Contacts of Syphilis Cases, Ven. Dis. Inform. **23**:323 (Sept.) 1942.

results from the first two or three efforts, with 71.4 per cent of the ultimate successes following the first effort (table).

Development of the venereal disease control program in the city of New York has resulted in the evolution of certain practical procedures and technics, which are detailed by Rosenthal and Goodman.[54] Effective case reporting with careful epidemiologic follow-up of infectious patients forms the cornerstone of the control program, although rehabilitation of infected selective service registrants and efforts to facilitate control of syphilis in industrial establishments have received considerable attention. A central tabulating unit has been found valuable in case holding and in contact investigation.

Case Holding.—A problem of control of syphilis more or less peculiar to that disease is the difficulty of keeping patients under treatment until adequate treatment has been effected. The reasons why patients become delinquent in their treatment and modalities of restoring them to treatment are exemplified by an analysis of 5,130 delinquencies.[55]

The reasons for delinquency were most often leaving the country, illness other than that due to treatment, working at the time of clinic sessions and

Successful Contact Investigations According to the Number of Epidemiologic Efforts Made (Packer, McGinnes and Puffer[55])

	Number of Contacts	Number of Successes	Cumulated Successes		
			Number	Per Cent of Total Contacts	Per Cent of Total Successes
Total	1,059	846	846	....	100.0
First effort	1,059	604	604	57.0	71.4
Second effort	306	157	761	71.9	90.0
Third effort	108	52	813	76.8	96.1
Fourth effort	45	23	836	78.9	98.8
Fifth effort	13	7	843	79.6	99.6
Sixth effort	5	3	846	79.9	100.0

reactions to treatment. In all, 38.2 per cent of these delinquent patients ultimately were restored to treatment. The type of follow-up effort that achieved the greatest success was a home visit in which the patient himself was interviewed. Of the patients who were restored to treatment by follow-up effort, 89 per cent were restored after the first effort and 98 per cent after the second effort. Additional efforts did not prove feasible.

Since Jan. 1, 1936, the law for premarital serologic tests for syphilis has been in effect in Connecticut. Talbot[56] has analyzed the results of the legal requirement for premarital blood tests over a seven year period. In this period, 750 men and 690 women were found to have positive reactions—a prevalence rate for both sexes of 14.1 per thousand marriages. About 50 per cent of the persons applying for marriage licenses who had positive serologic reactions and were given a diagnosis of syphilis were not aware of the infection. Since the law has been in operation, the number of cases of congenital syphilis in the state has decreased progressively. The marriage rate per thousand population decreased

54. Rosenthal, T., and Goodman, H.: Epidemiologic Methods Used in the Control of Venereal Diseases in New York, New York State J. Med. **42**:1346 (July 15) 1942.

55. Packer, H.; McGinnes, G. F., and Puffer, R. R.: A Study of Delinquent Syphilis Patients in the Memphis-Shelby Venereal Disease Control Program, Ven. Dis. Inform. **23**:289 (Aug.) 1942.

56. Talbot, H. P.: Blood Tests for Syphilis on Premarital Applicants for Seven Year Period, 1936-1942, Connecticut Health Bull. **57**:70 (March) 1943.

in 1936, the first year the law was in effect, but since then has increased steadily, to become more than twice as great in 1942 as in 1932.

The author considers the law effective: as a case-finding procedure; as setting a precedent for physicians and furnishing an incentive for making routine serologic tests; as a measure for reducing the incidence of congenital syphilis, and as a means of educating the general public about syphilis.

Mahoney [57] outlines the approved manner of complying with the provisions and requirements of the statutes in force in various states in regard to premarital blood testing. Twenty-nine states require premarital blood tests. Those states which do not are: Alabama, Arizona, Arkansas, Delaware, District of Columbia, Florida, Georgia, Idaho, Kansas, Maryland, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Mexico, Oklahoma, South Carolina and Washington. Of the states demanding a premarital blood test, all will accept a single standard or acceptable test with the exception of Pennsylvania, which requires that both a flocculation and a complement fixation test be employed.

The following states will accept reports of serologic tests performed in the laboratories of the armed services and of the United States Public Health Service and will permit the commissioned medical officers of the services to collect the specimens of blood and perform physical examinations: California, Colorado, Indiana, Iowa, Michigan, New Jersey, New York, Rhode Island, South Dakota, Utah, Vermont, and Virginia. Information regarding the requirements of the other states demanding premarital tests is variable. A brief digest of the requirements of each is given in the present article.

Serologic Surveys.—In control of syphilis, methods of case finding which have a wide field of application and which bring under treatment a large number of infectious persons are those which should be stressed. As Packer [58] points out, the method or combination of methods which will achieve this end most effectively in any community can be determined best by actual application and subsequent analysis of the results. Each community has its own peculiar population characteristics and its own problems with regard to case finding. The author's experience in Memphis and Shelby County, Tenn., indicates that in areas of high prevalence of syphilis, particularly when a considerable proportion of the population is Negro, the group approach through routine examination of large sections of the population should be stressed.

Serologic surveys have been widely used as a means of discovering cases of syphilis. Such surveys provide a method for determining the prevalence of syphilis in selected population groups. They serve also as a valuable medium of education. Many different groups have been surveyed by routine blood tests. In surveys among labor groups the usual procedure is for the employer to act as the sponsoring agent. Koch and Merrill [59] report the results of a survey in which the approach was made through the labor organization without reference to employer groups. Serologic tests were entirely voluntary, and of the total union membership in the areas surveyed, only 4 per cent had tests made. Of 8,027 persons tested, 336 (4.1 per cent) were found to have positive serologic reactions. Of 133 of this number fully studied, 71.5 per cent were persons whose infections

57. Mahoney, J. F.: Requirements of Premarital Legislation as They Apply to the Laboratories and Commissioned Medical Officers of the Armed Services and of the United States Public Health Service, Ven. Dis. Inform. **24**:105 (April) 1943.

58. Packer, H.: A Comparison of Case-Finding Methods in a Syphilis Control Program, Ven. Dis. Inform. **23**:440 (Dec.) 1942.

59. Koch, R. A., and Merrill, M. H.: Serologic Survey Among Labor Unions in Northern California, Ven. Dis. Inform. **23**:317 (Sept.) 1942.

were newly discovered. The costs of the survey were recorded. For each previously unknown case of syphilis discovered the cost was approximately $42.

Because of wartime demands for blood plasma, more serologic tests for syphilis than ever before are being performed on prospective blood donors. Noting the case finding value of these tests, Frye, Keller, and Kampmeier [60] have sought to determine by the questionnaire method what is being done about the donors found to have positive or doubtful reactions. Of 603 hospitals from which replies to the questionnaire were received, 6.5 per cent did not test blood donors for syphilis before their blood was used. Of those hospitals testing donors, 12.5 per cent had no method for notification of the donors found to have positive or doubtful reactions. The person or agency responsible for notifying donors and the method of notification varied according to the size of the hospital and the type of administrative control. Most commonly, responsibility for notification of donors devolved on the private or attending physician.

The findings indicate the need in many hospitals for a more definite system whereby prospective blood donors found to have positive or doubtful serologic reactions for syphilis may be notified of the result of the test in order that they may receive prompt and adequate examination and treatment. The authors recommend that hospitals report such persons to the responsible health department as suspected of having syphilis. The health department then could arrange for proper disposition.

State Consultation Service.—When organizations for control of syphilis depend to a great extent on the private practitioner to uncover most and treat about half of the existing persons with syphilis, any procedure that holds promise of improving their role must be seriously considered. The provision of consultation service along definitely formulated lines offers an opportunity in this regard. Because of the magnitude of the task, the health department is the proper agency to assume the responsibility of providing the service.

Within the past few years there has been a trend toward the creation or improvement of existing facilities for furnishing syphilis consultation services to private physicians. Four state health departments already have provided this service by incorporating full time consultants within their divisions of venereal disease control. Kroll [61] has analyzed the operation and results of this service in the state of New York. An intensive consultation service properly decentralized and actively promoted gave promising results. Of 826 physicians apprised of the availability of the service by letter, 105 responded by indicating their desire for consultation. Assistance was readily accepted by an additional 218 physicians of a total of 334 who were visited without invitation.

Questions most frequently asked of the consultants were those involving late latent syphilis, drugs and neurosyphilis. Questions on early syphilis, congenital syphilis, interpretation of serologic reports, infectiousness, pregnancy and cardiovascular syphilis were frequent in the order named.

Role of the Pharmacist in Syphilis Control.—An editorial writer,[62] discussing the role of the pharmacist in control of venereal disease, states:

> The pharmacist himself is more aware than anyone else of his responsibility to the community in assisting the health authorities in the urgent task of bringing venereal disease

60. Frye, W. W.; Keller, A. E., and Kampmeier, R. H.: The Hospital and the Syphilis Problem in Prospective Blood Donors, J. A. M. A. **121**:182 (Jan. 16) 1943.

61. Kroll, M. M.: A State Syphilis Consultation Program for Private Practitioners, Am. J. Syph., Gonor. & Ven. Dis. **27**:63 (Jan.) 1943.

62. Venereal Disease Control and the Pharmacist, editorial, New England J. Med. **227**: 888 (Dec. 3) 1942.

patients under proper treatment. . . . Through his professional organizations, notably the American Pharmaceutical Association, and with the cooperation of the American Social Hygiene Association, the pharmacist has demonstrated a willingness to take an active part in the national program for the control of syphilis and gonorrhea.

By participating in the program for venereal-disease control . . , the pharmacists of this country will strengthen public confidence in their profession. At the same time they will know personally that their efforts are being given toward the elimination of the venereal-disease scourge, both for the best interests of the civilian population and for the greater fighting efficiency of the armed forces of the Nation.

SYPHILIS AND THE WAR

Wartime Venereal Disease Control: Civilian Aspects.—In the wartime program for control of venereal disease, Americans are, as Vonderlehr [63] indicates, well prepared, since the fundamental principles of control already have been establishd. It remains necessary, however, to apply these principles promptly and fully, that the campaign be aggressive and unified and that there be unanimous support of the public, of the medical profession and of the public health groups.

As minimal services, the health department must supply: collection and analysis of morbidity data; adequate laboratory services; an effective control program for industry; organization and supervision of clinic services and epidemiologic procedures; adequate follow-up services for men examined under the Selective Service System; utilization of routine serologic tests as a case finding procedure; development by means of an effective educational program of the support and understanding of the public and of all interested scientific groups, and encouragement and support for law enforcement agencies in the repression of prostitution.

The physician who manages patients with venereal disease privately or in the clinic must provide for treatment to obviate infectiousness and for the examination of contacts. The weakest links in the venereal disease control program, according to the author, are case finding through routine epidemiologic procedures, and case holding until the treatment has been completed. A greater number of adequately trained follow-up workers clearly is needed.

The role of the Army and the Navy in control of venereal disease includes: provision for qualified professional personnel; abolition of punitive measures for the acquisition of venereal disease; modification of the policy of compulsory hospitalization for uncomplicated venereal disease; educational measures; supervision of prophylaxis, and cooperation with other interested groups within the post and in the civilian community. The public-spirited citizen interested in social hygiene also contributes to the success of the program, chiefly by fostering general understanding and support through educational methods.

Vonderlehr [64] further describes some of the problems occasioned by the venereal diseases in time of war. Provisions for early diagnosis and facilities for the institution of prompt treatment exist in almost all areas with full time local health services, but a scarcity of trained personnel has handicapped the follow-up program. The routine serologic examination of selectees has placed an additional strain on epidemiologic facilities, for the pressing need for men necessitates prompt rehabilitation. It is the obligation of the health officer and the physician in private practice to bring the infected selectees under treatment. Vonderlehr says:

In all history, war has opened the gates to pestilence. Venereal disease strikes first, and its wounds are often the last to heal. At the present time, the United States is better prepared

63. Vonderlehr, R. A.: Individual Support in the Unified Wartime Venereal Disease Control Program, Am. J. Syph., Gonor. & Ven. Dis. **26**:661 (Nov.) 1942.

64. Vonderlehr, R. A.: The Impact of the War on the Venereal Disease Problem, New England J. Med. **227**:203 (Aug. 6) 1942.

than ever before to wage an effective campaign against gonorrhea and syphilis. Tolerated prostitution and failure to apply promptly modern medical knowledge are the most vulnerable points in this field of medicine.

Stressing the relationship between the practicing physician and the health department in control of venereal disease in wartime, Vonderlehr [65] indicates that the emergency problem is to get infected selectees and their contacts in condition for military service and essential war work in the shortest time possible. The health department should teach the public the causes, the prevention and the treatment of venereal diseases; provide laboratory services and drugs; keep persons known to be infected under treatment by private physicians or at clinics; seek out persons who are sources of infection and bring them under treatment; treat those who cannot afford to pay and refer to practicing physicians all who can. The physicians, for their part, are asked to educate and treat their patients, to be ever on the alert for contacts and to report lapses from treatment as quickly as they occur.

Emerson [66] pessimistically writes:

> We may expect in the civilian as in the military population an increase in the direct and indirect effects of . . . syphilis in this wartime unless there is something like a revolution in the social attitudes toward . . . venery. Every . . . syphilitic person is an obstruction to military and civil preparedness for national defense.

The author notes that the specific death rate among "our industrial and wage earning men and women and their families," the death rate per hundred thousand from syphilis, has decreased from 19 to 9.0 in the past twenty-five years. The material from which these statistical data were derived are not apparent from the article, but to the reviewers it seems unlikely that such precise figures can be delineated.

According to Aselmeyer,[67] the two conditions resulting from the war which overshadow other considerations in the venereal disease control program are: (1) the extraordinary mobility of both military and civilian populations and (2) the acute shortage of professional personnel in civilian areas. Outlining the venereal disease control measures at present available, the author stresses the role of the civilian physician, stating:

> The war will bring to the physicians who remain in their communities overwhelming tasks comparable with the experiences of our colleagues in the Army and Navy. One of the first tasks commanding the doctor's attention is the control of venereal diseases in his community. No matter how well we plan and execute a national attack, no matter how far we stretch the available funds, the control of these diseases is in the hands of the local physicians of the United States. Neither the federal government nor the local health department nor the private physician, however, can accomplish this great task alone. Together, we can bring venereal diseases under control and keep them under control. . . .

Certain problems concerned with the control of venereal disease in wartime have been discussed by Stokes,[68] to whom the application of recent scientific discoveries to the control program seems paramount. The fallibilities of serodiagnostic tests and of dark field examination, intensive arsenotherapy, rapid cure of gonorrhea with sulfonamide compounds and mechanical and chemical prophylaxis are all discussed, together with the problem of morale as it relates to venereal disease.

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65. Vonderlehr, R. A.: Public Health Control of Venereal Diseases in the District of Columbia, M. Ann. District of Columbia **11**:471 (Dec.) 1942.

66. Emerson, H.: Civilian Health in War Time, J. A. M. A. **119**:1389 (Aug. 22) 1942.

67. Aselmeyer, A. J.: Civilian Measures for the Control of Venereal Diseases in World War II, J. A. M. A. **120**:880 (Nov. 21) 1942.

68. Stokes, J. H.: The Wartime Control of Venereal Disease: Problems in the Application of Recent Scientific Discoveries, J. A. M. A. **120**:1093 (Dec. 5) 1942.

Rehabilitation of Selectees.—An inquiry [69] to determine how many selectees rejected because of venereal disease have been put under treatment and after treatment have been inducted into military service has been made by the United States Public Health Service. Thirty-three states report that of the 178,884 syphilitic selectees who were rejected, 114,337 (64 per cent) were under treatment on Dec. 31, 1942. Of these, 81,632 had been placed under treatment as a result of the selectee examination, and the remaining 32,705 had already been receiving therapy. The states report that 5,777, or 5 per cent of the total number under treatment, have been inducted.

Role of the Public Health Nurse.—The role to be played by the public health nurse in wartime control of venereal disease has been described by Pearce.[70] As increasing numbers of physicians are drawn into the armed forces, nurses will be called on to perform under medical supervision more of the duties and functions normally carried out by doctors. The demand for nurses will be augmented with the development of artificial fever therapy and of rapid treatment schedules for antisyphilitic therapy.

To insure economical use of nursing personnel, Miss Pearce recommends: (1) the release of the public health nurse from many clerical and housekeeping duties through the use of volunteer or paid clinic assistants; (2) the employment of inactive nurses to assist with treatment; (3) the assignment of a minimum number of public health nurses or medical social workers; (4) increased emphasis on special consultative and educational services.

Because of the increased importance of venereal diseases in time of war, Burke[71] believes that all public health nurses should spend at least part of their time in tracing contacts. Discussing the objections which have been raised to the use of general public health nurses in venereal disease control, she concludes that it is highly desirable for the general nurse to supplement the work of the specialized nurses already in the field.

Of paramount importance in wartime venereal disease control are follow-up and rehabilitation of selectees rejected for armed service because of syphilis. The ways in which the nursing profession can assist in this work are discussed by Burns.[72]

In interviewing the patient with syphilis, it is important, according to Bailey,[73] to establish between the patient and the clinic a rapport on which lasting confidence may be developed. The patient must sense a regard for his own welfare as well as for the welfare of others. When the persuasive approach has won the patient's confidence, he will cooperate in getting his contacts examined.

Wartime Venereal Disease Control: Military Aspects.—An extensive and important review concerned with the prevention of venereal diseases in the Army of the United States has been made by Siler.[74] The first section of this monograph is a statistical review of the incidence rates and prevalence of the venereal infections in the Army. The second section concerns the preventive measures initiated within the Army in years past for the control of these diseases. Of greatest interest

69. U. S. Public Health Service, Association Notes, Mil. Surgeon **92**:675 (June) 1943.
70. Pearce, D.: Major Public Health Battlefront, Pub. Health Nursing **35**:8 (Jan.) 1943.
71. Burke, M. A.: Extra-Familial Contact Tracing, Pub. Health Nursing **35**:15 (Jan.) 1943.
72. Burns, A.: Syphilis Follow-Up Among Selectees, Pub. Health Nursing **35**:28 (Jan.) 1943.
73. Bailey, F. G.: Interviewing the Syphilis Patient, Pub. Health Nursing **35**:47 (Jan.) 1943.
74. Siler, J. F.: The Prevention and Control of Venereal Diseases in the Army of the United States of America, Army M. Bull., May 1943, no. 67.

are Siler's comments on the practical value of the various control measures which have been tried during the past thirty years.

According to Turner,[75] the present venereal disease rates in the Army are substantially below those of World War I and only slightly higher than the rates for the preceding ten years of peace, but the rate of 40 per thousand for 1941 and the somewhat lower rate for 1942 are still excessive. There are still too many soldiers being infected and too many selectees reporting for duty with venereal disease. During the past two and a half years many important steps have been taken to mobilize the health forces of the country, both military and civilian, to meet this problem. In 1940, the so-called eight point agreement was signed. In the same year, the United States Public Health Service assigned a liaison officer to the headquarters of each service command to aid in the control of venereal diseases. In April 1941, the Social Protection Section, Defense Health and Welfare Services, was organized, and later the Interdepartmental Liaison Committee on Venereal Diseases was created. This committee comprises representatives of the Army, the Navy and the Public Health Service, the Social Protection Section and the American Social Hygiene Association. Early in 1942 authorization was given for the assignment of specially trained venereal disease control officers to major headquarters of the Army. Never before in the history of this country has the stage been so well set for a concerted attack on these diseases.

It has been learned that the control of venereal disease among troops must be a collaborative effect between military and civilian authorities. The problem is primarily one of preventive medicine, the immediate task being to keep soldiers and workers well and effective. It is agreed that commercialized prostitution is a breeder of venereal disease and should go. Remarkable progress has already been made during the past two years in suppressing the most obvious and perhaps the most dangerous type of prostitution, that centered in the redlight district and the brothel.

It is becoming increasingly evident that other forms of social misbehavior are beginning to play a prominent role in the spread of venereal disease. An ever increasing proportion of soldiers are being infected by pick-ups, tavern and dance hall girls and the like. It is difficult to know just who is and who is not a prostitute. The important element in the picture is not the individual woman but the business structure which makes it possible for a girl to expose numerous contacts. Turner says:

> To express this idea, Dr. Donald Williams, of British Columbia, has coined a new phrase, "the facilitation process." He maintains, and rightly, I believe, that we should cease speaking of prostitution in this connection, and concentrate our social and legal efforts on finding and suppressing the "facilitators"—the tavern keepers, the bell boys, the taxi drivers, and the owners of these businesses who facilitate the spread of venereal disease.

This approach appeals to Turner, who has been disturbed by the tendency in some places for law enforcement officials, often at the instigation of those concerned in control of venereal disease, to engage in a determined hunt for young girls to the exclusion of the more important job of getting at the facilitators.

A program for venereal disease control in a military camp is outlined by Lieberman,[76] who discusses education, prophylaxis, case finding, treatment, cultivation of cooperation with civilian agencies and establishment of cooperative relations with the military police and recommends certain desirable administrative measures.

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75. Turner, T. B.: Some Aspects of Venereal Disease Prevention in Wartime, J. Social Hyg. **28**:518 (Dec.) 1942.

76. Lieberman, B. A.: An Effective Military Venereal Disease Control Program, War Med. **3**:174 (Feb.) 1943.

Worthy of special comment are the data presented on the efficiency of station prophylaxis. The author states:

> Statistics available to me covering approximately 500,000 troops for the first half of 1942 indicate that only 0.69 per cent of prophylactic treatments were ineffective in preventing the development of venereal disease in exposed soldiers.

It is perhaps pertinent to object to the inclusion of the infected soldier's name on the contact report forwarded to the civilian health department. Moreover, the practice of collecting information on contacts at prophylactic stations should be condemned, since it tends to dissuade men from taking prophylaxis. The program outlined, however, is one which should effectively lower the incidence of venereal infections in military establishments.

Educational Talks to Service Personnel.—All medical officers are charged with instructing the entire personnel regarding the nature of venereal disease and warning them of the dangers therefrom. One of the most effective measures for education on venereal disease is a well planned and well delivered man-to-man discussion by the medical officer himself.

Reynolds [77] discusses the salient features of educational talks to service personnel on venereal disease. The most effective appeals are to the men's sense of reasonableness and to their fear of the consequences of venereal infection. In outline, the talk should include an appropriate introduction, a brief description of the genitoinfectious diseases, discussion of the common misconceptions about these diseases, explanation of how and from whom venereal infections are acquired and spread, complete details of how they may be prevented and instruction on what to do if infection is suspected. A catalog of venereal disease educational materials available to medical officers is appended.

Chemical Prophylaxis.—It is well established that venereal infections can be prevented in most instances by proper chemical prophylaxis. This fact is amply attested by the experiences of the Army and Navy. On the other hand, the failure of chemical prophylaxis in American civilian groups apparently is taken for granted. Civilians fail to avail themselves of prophylaxis because of inconvenience, fear of publicity or embarrassment, and lack of compulsion.

Frantz [78] believes successful chemical prophylaxis of the venereal diseases in the American civilians to be highly desirable. In August 1941, the Sacramento (Calif.) City Health Department opened an experimental prophylaxis station for civilians and military use. Between Aug. 14 and Dec. 14, 1941, 4,163 standard chemical prophylactic treatments were administered. Male civilians received 2,062 (49.5 per cent) and members of the armed forces 2,101 (50.5 per cent) of these treatments. No coercive measure were used. Both the civilian and the soldier attended the same station concurrently and were served by the same attendant. Certain minimal data were secured from each person receiving prophylaxis: initials, time of exposure, time of prophylaxis, name of the consort and place of exposure. Ninety-six per cent of the group named a prostitute as the consort. The community reaction to the establishment of the station was favorable. Hotels, theaters, gasoline stations and civic institutions have permitted the posting of advertising material in their rest rooms.

Control of venereal disease in the armed forces depends to a high degree on effective chemical prophylactic treatment that may be used after sexual inter-

77. Reynolds, F. W.: Suggestions to the Naval Medical Officer for Talks on Venereal Disease, U. S. Nav. M. Bull. **41**:889 (May) 1943.

78. Frantz, R.: Civilians, Soldiers and the Chemical Prophylaxis of Venereal Diseases, Ven. Dis. Inform. **23**:286 (Aug.) 1942.

course. One of the difficulties with this treatment is that it may not be available near the place where the exposure occurs. This fact, together with certain other objectionable features of "station" prophylaxis, has led medical officers to study the use of prophylactic kits.

Pelzman and Still [79] report that the prophylactic packet used at Fort Belvoir, Va., contains a soap-impregnated wash cloth, a tube containing silver picrate jelly (0.25 per cent), a tube with a mild mercurous chloride ointment and a cloth bag to protect the clothing. In their small series of 374 soldiers who were given prophylactic treatment with these packets, no infections with syphilis developed within eight weeks. The authors believe that packet prophylaxis of venereal infection compares favorably with prophylactic treatment administered at prophylactic stations.

Contact Reporting and Examination.—An important phase of control of venereal disease is the discovery of unrecognized infections, especially those in the early and communicable stage. Experience has shown that the search for unrecognized infections is especially productive among persons who have had intimate contact with infected persons.

A summary of contact reporting from the point of view of the medical officer is made by Reynolds.[80] The proper reporting of the sexual contacts of service personnel infected with venereal disease presupposes a knowledge of the reasons why the names of contacts are withheld and requires a tactful sympathetic approach to the patient. Care must be taken to differentiate "source of infection" from "sexual contacts." A contact is defined as a person whose exposure to a patient during the period of possible infectiousness has been sufficiently intimate as to subject either to risk of acquiring the disease. Reports should contain as much information as possible about each contact and should be forwarded to the responsible civilian authorities as soon as practicable.

An analysis of the data obtained by questioning infected service personnel at a large Army post is summarized by Barnes.[81] Of 1,032 patients with venereal disease, 26 per cent divulged the full name of the sexual partner, and an additional 15 per cent gave the first name only. The majority (50 per cent) of contacts named were "pick-ups" or free-lance prostitutes, and only 26 per cent were girls in organized houses of prostitution. Hotels most often were the places where exposure occurred, with automobiles and private homes next in order of frequency. Gonorrhea occurred five times as often as syphilis, and 9 of each 10 men acquiring one or the other infection had neglected to take prophylactic treatment. Over half of the men said they had had a prior infection in civil life.

The information obtained was used to determine where most of the infections were originating. It served as a guide to the need for additional prophylactic stations and made it possible to call to the attention of the civil police authorities the need for enforcement of local laws against commercialized and clandestine prostitution.

Effective control of venereal diseases in the armed forces requires close cooperation between the service organizations and civilian health agencies. In no way is this mutual assistance better exemplified than in the epidemiologic investigation of the sexual contacts reported by infected service personnel.

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79. Pelzman, I. A., and Still, J. W.: Packet Type of Kit for Venereal Disease Prophylaxis: Preliminary Report Concerning Its Use, War Med. **3**:474 (May) 1943.

80. Reynolds, F. W.: Contact-Reporting in Venereal Disease Control: A Function of the Medical Officer, Mil. Surgeon **91**:432 (Oct.) 1942.

81. Barnes, A.: Sources of Venereal Infections at an Army Post: Study of 1,032 Cases at Fort Leonard Wood, Mil. Surgeon **92**:257 (March) 1943.

A novel experience in contact questioning is reported by Howard, Vahey and Wetherby.[82] In Massachusetts, health department nurses trained in epidemiologic methods were allowed to enter Army camps and Navy stations to question infected personnel as to their sexual contacts. This expedient proved effectual, for whereas previously medical officers had obtained adequate information in only 13 per cent of the cases, the public health nurses were successful 60 to 83 per cent of the time.

The data so gathered were analyzed and utilized by the health department for further study. When the information implicated prostitution or an allied activity requiring police control, it was forwarded to the responsible police agency. Of 193 contacts followed by the nurses, 89.6 per cent were found and placed under medical observation; 36.3 per cent of the 157 referred to the police were apprehended. Two hundred and seventy-three contacts were referred to other state health departments, and 27.5 per cent were found successfully (evidence of reasonably good cooperation among the state health departments).

An analysis[83] of venereal disease contacts reported from four states in the Ohio River Valley for the period ending July 31, 1942 suggests that the size of a city contributes more to the frequency of infection among military personnel than does its proximity to an Army camp. The data indicate that the highest rate is among cities of 100,000 population and over, and that rates in smaller cities decrease with the size of the city. Some of the largest cities were as much as 150 miles (240 kilometers) from a military establishment but were reported, nevertheless, as localities where many infections were contracted. Thus the role of modern transportation facilities is indicated and the necessity for a nation-wide control program emphasized.

SYPHILIS IN FOREIGN COUNTRIES

England.—In England,[84] a new defense regulation (33B) extends the powers available under the present law for the treatment of venereal diseases and enables compulsion to be applied in carefully defined circumstances.

Hitherto the arrangements for the treatment of these diseases have been based on voluntary attendance for treatment. The new regulation leaves the voluntary basis unchanged, but provides for compulsion, where necessary, to bring under treatment those persons who are impervious to methods of education and persuasion and who refuse to attend voluntarily for treatment although known to be infected and to be spreading infection.

Commenting on England's new Defense Regulation 33B, whereby persons suspected of spreading venereal disease are compelled to undergo examination and treatment, the London correspondent of *The Journal of the American Medical Association*[85] writes:

> In contrast with the compulsory treatment of venereal disease in other countries, the arrangement in this country has been based exclusively on voluntary attendance. This is in accordance with that respect for the freedom of the individual which is characteristically British. But here the obvious criticism is that what is granted is freedom to spread disease. The voluntary system has had a large measure of success, and before the war the incidence

82. Howard, E. B.; Vahey, V. V., and Wetherby, U. V.: Epidemiologic Investigation of Syphilis and Gonorrhea in the Army and Navy in Massachusetts, Ven. Dis. Inform. **24**:1 (Jan.) 1943.

83. Venereal Disease Contacts, Association Notes, Mil. Surgeon **91**:712 (Dec.) 1942.

84. Chronic Sources of Venereal Infection: Power to Enforce Treatment, War Medicine Series, Brit. M. J. **2**:616 (Nov. 21) 1942.

85. Compulsory Treatment for Venereal Disease, Foreign Letters (London), J. A. M. A. **121**:142 (Jan.) 1943.

of venereal disease was low and compared favorably with that of other countries. The war has now accustomed us to limitation of our freedom in many directions, and for good reason a new defense regulation introduces compulsion for the treatment of venereal disease in certain carefully defined circumstances.

The regulation provides that persons named by two separate patients under treatment as the suspected source of their infection can be required, by notice served on them by the health officer of the district in which they live, to attend for examination, and if necessary, for treatment by a "special practitioner," and to continue treatment in accordance with his directions until they are certified as free from venereal disease in a communicable form. . . .

Those interested in details of Regulation 33B are referred to a comprehensive discussion of the legal aspects of the act by Shannon.[86]

Puerto Rico.—According to Quintero,[87] syphilis is about two and a half times as prevalent in Puerto Rico as in the continental United States. The socioeconomic structure of the island is considered important in this high rate of prevalence. Overcrowding, poverty and illiteracy all are factors. Under the existing circumstances, a high incidence rate of syphilis among service personnel stationed in Puerto Rico is to be expected. To meet the situation, the author recommends expansion of the control program in its medical, educational and legal aspects. Intensification of the program for follow-up of reported contacts, isolation of patients for intensified treatment and repressive measures against prostitution are advocated.

Soviet Russia.—A report of the Anglo-Soviet Medical Council[88] says that venereal diseases were widespread in tsarist Russia, especially among the population of the national minorities. In Moscow in 1914 there were for every 10,000 people approximately 388 patients with venereal disease, of whom 56.9 per cent had been infected by prostitutes. Incomplete data indicate that in the country as a whole there were 76.8 persons with syphilis per 10,000 people.

With the advent of Soviet power, one of the earliest public health measures was to institute a campaign against venereal diseases. There were two main directions of attack, against venereal diseases as such and against prostitution as an institution. From the Soviet point of view, prostitution is regarded as being primarily due to economic causes, and the campaign to abolish it was directed against the institution, not the individual. Two new laws were passed, one making the infecting of a sexual partner punishable by up to three years' imprisonment and the other making treatment compulsory. Treatment centers were established; graduate courses of instruction for physicians were organized, and serologic tests were used widely. As a result of these measures, there has been a considerable decrease in the incidence of infection throughout the country.

Australia.—Statistics prepared at the 120th Australian Special Hospital over a period of eighteen months show that 85 per cent of the patients infected with venereal disease contracted their infection from amateur sources and 15 per cent from professional prostitutes. The great majority of patients contracted the disease while on leave in one of the larger cities.

As to the prevention of venereal disease among the Australian armed forces, Gibson[89] says that Army medical officers are being given lectures by specialists at the Army School of Hygiene and the School of Public Health and Tropical Medicine. Lectures are also given to combatant officers and noncommissioned

86. Shannon, N. P.: The Compulsory Treatment of Venereal Diseases Under Regulation 33B, Brit. J. Ven. Dis. **19**:22 (March) 1943.

87. Quintero, E.: Preliminary Report on Local Venereal Diseases Relative to the Puerto Rico Encamped Military Forces, Bol. Asoc. méd. de Puerto Rico **35**:180 (May) 1943.

88. Anti-Venereal Measures in the Soviet Union: Report from the Anglo-Soviet Medical Council, Brit. J. Ven. Dis. **19**:39 (March) 1943.

89. Gibson, N. M.: Control of Venereal Disease in the Army, M. J. Australia **2**:290 (Sept. 26) 1942.

officers, who in turn are expected to impart this knowledge to the troops of their units. A meeting attended by the commonwealth and state authorities, together with the representatives of all services, including the United States Army, is held once a month to discuss prophylaxis and treatment as well as coordination between the services.

Condoms and chemical prophylactic kits are issued free to all troops going on leave. The prophylactic packet contains two tubes, one containing 3 per cent mild protein silver jelly, and the other 33 per cent mild mercurous chloride ointment. Prophylactic stations have been established in all camps and nearby towns and cities. Special medical inspection is made of all troops entering the camp and before they go on draft, as well as at various times during their training. Soldiers found to be infected are evacuated to the 120th Australian Special Hospital. All soldiers in the Home Forces suffering from syphilis are discharged as medically unfit, since it is considered necessary to treat them for eighteen to twenty-four months.

France.—According to *Transocean France* of March 16, 1943,[90] 2,000,000 Frenchmen have died from venereal disease during the past ten years, and some 5,000,000 Frenchmen are infected with syphilis today. Dr. Arthur Vernes has declared that during the last three years alone infections have trebled.

Infant mortality in France during 1940[91] was 9.1 per cent. In the same year 25,000 stillborn children were delivered, a large percentage of these stillbirth cases being due to syphilis.

SYPHILIS AND INDUSTRY

Control of Venereal Disease in Industry.—A venereal disease control program in industry involves cooperation among four groups: the employers, the employees, the physicians and the public health department.

The objectives of a venereal disease control program in industry, as outlined by an advisory committee to the United States Public Health Service, are reported by Anderson and his co-workers.[92] Responsibilities of the medical and public health professions include: case finding and disposition of all cases of venereal disease among workers in industry; the establishment of equitable policies for the employment of applicants and continuation of services of infected employees, and coordination of the community and industrial programs for venereal disease control. The objectives for the employees are to improve the physical condition of employees, to reduce the number of work days lost through illness or injury, to provide proper job placement for infected men, and to prolong and increase the earning power of employees by increasing life expectancy. For the employers, the program should reduce compensation costs, lessen work interruptions and labor turnover, enhance production by increasing the efficiency of workers and minimize those personnel problems which arise from syphilis and gonorrhea as causes of ill health and nervous instability.

Responsibility for the administration of the program should be shared by the industrial hygiene and venereal disease divisions of the state health department. The educational program should be integrated and correlated with the general program of health instruction. Examinations for venereal infections should be part of the general physical examination, and the results of the examination should be confidential.

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90. Public Health Under Hitler, J. A. M. A. **122**:451 (June 12) 1943.
91. Public Health Under Hitler, J. A. M. A. **122**:516 (June 19) 1943.
92. Anderson, O. L.; Clarke, W.; Dreesen, W. C.; Hayhurst, E. R.; Holmblad, E. C., and Peterson, C. M.: Venereal Disease Control Program in Industry, J. A. M. A. **120**:828 (Nov. 14) 1942.

In the opinion of the advisory committee:

There is no reason for denying employment to an applicant or for discharging an employee because an examination has revealed evidence of syphilis or gonorrhea, provided:

1. That the employee agrees to place himself under competent medical management.

2. That, if the stage of the disease is infectious, employment should be delayed or interrupted until such time as a noninfectious state is established through treatment and open lesions are healed.

3. That syphilis exists in a latent stage.

4. That, when disabling manifestations exist which would render such individuals industrial hazards to themselves, other employees or the public, employment may be deferred or denied.

5. That provision be made, whenever possible, for occupational readjustments of employees who develop disabling manifestations that do not incapacitate them from performing some type of useful work.

6. That workers with syphilis in any of its stages, and regardless of past or present treatment status, should be excluded from areas of toxic exposure, and that those having cardiovascular syphilis or neurosyphilis should not be exposed to such physiologic stresses as extremes of temperature, strenuous physical exertion or abnormal atmospheric pressure.

7. That workers with gonorrhea should be allowed to work only under special medical observation during the administration of sulfonamide drugs.

In making educational material on venereal diseases available to industrial employees, Storey [93] believes the approach should be made through: (1) plant facilities; (2) community facilities; (3) labor organizations; (4) courses or classes or schools that prepare prospective employees for skilled service in factories, and (5) public school and college student health programs.

Stressing the dangers of ill advised and improperly directed attempts to extend control of syphilis to industry, Nelson [94] says:

Any physician who has under his care an employable syphilitic, and the industrial physician in particular, holds in his hand the future of the infected with syphilis. In those industries in which the problem is handled intelligently (and it is comforting to know that the number is constantly increasing) sound medical advice deserves much of the credit. How soon the problem is to be solved in the others will depend upon whether the well-informed physician or the uninformed layman is to determine the medical policy. It is becoming nauseatingly tiresome to note the frequency with which lay officials and directors, not only of industry but of hospitals and institutions and public agencies, lay down the rules as to who shall be admitted to employment, and even as to who shall be admitted as patients; not on the basis of well-known medical fact, but on the basis of prejudice, taboo and popular misconceptions. If we cannot look to the medical profession for the correction of this intolerable situation, to whom, then, may we look?

DRUGS

Dichlorophenarsine Hydrochloride. — Dichlorophenarsine hydrochloride (3-amino-4-hydroxyphenyldichloroarsine hydrochloride) has been used experimentally in the treatment of syphilis at Vanderbilt University Hospital, and the results of the study are reported by Kampmeier and Henning.[95] Over four thousand injections were given to 251 syphilitic patients. After a single therapeutic dose 42 of 45 patients with infectious lesions had negative results of dark field examination within twenty-four hours. Healing of acute lesions was prompt, chancres healing within four weeks and secondary lesions within five weeks. Serologic reactions became negative at a time comparable to that with use of other arsenical preparations.

93. Storey, T. A.: Educational Hygiene—Extension to Industrial Employees for the Control of Gonorrhea and Syphilis, Indust. Med. **11**:411 (Sept.) 1942.

94. Nelson, N. A.: Syphilis in Industry, Am. J. Syph., Gonor. & Ven. Dis. **27**:73 (Jan.) 1943.

95. Kampmeier, R. H., and Henning, H. B.: Treatment of Syphilis with Chlorarsen, Am. J. Syph., Gonor. & Ven. Dis. **27**:208 (March) 1943.

No serious untoward reactions were encountered. Nausea, vomiting and diarrhea were the most common reactions. The study indicates that phenarsine hydrochloride is effective in acute syphilis, is attended by few reactions and may be used as an alternate drug for patients having reactions to other arsenical drugs.

Ninety-six patients with syphilis, 20 of whom had either primary or secondary syphilis, were given by Long [96] a total of 2,033 injections of dichlorophenarsine hydrochloride. The compound was used as a mechanical mixture of 1 part by weight of 3-amino-4-hydroxyphenyldichloroarsine hydrochloride and 3⅓ and ⅓ parts of sodium citrate added as a buffer. It is readily soluble in water, salt solutions and dextrose solutions. The arsenical portion of this mixture contains 25.8 per cent of arsenic, while the final mixture contains 5.96 per cent. When dichlorophenarsine hydrochloride is dissolved in water the p_H of the solution is approximately 5.2, and the chlorine atoms are hydrolyzed so that when the drug is injected it is essentially arsenoxide. The drug was found to be effective in the treatment of early syphilis. Spirochetes could not be found in primary lesions twelve hours after the first dose. Serologic tests of the blood for syphilis responded satisfactorily; there was a low incidence of abnormal spinal fluids among the patients with early syphilis. Toxic reactions were limited to mild gastrointestinal disturbances. None of the severe forms of toxic reactions were noted.

For a period of eighteen months dichlorophenarsine hydrochloride has been studied at the University of Pittsburgh. As to the chemistry and pharmacology of the drug, Guy, Goldmann and Gannon [97] say:

> Two single dosage forms of phenarsine [dichlorophenarsine] hydrochloride are available. The smaller dose contains 0.045 Gm. of 3-amino-4-hydroxyphenyldichloroarsine hydrochloride, which yields 0.0308 Gm. of the active principle, 3-amino-4-hydroxyphenylarsenoxide (arsenoxide). A dose of 0.04 Gm. of mapharsen yields exactly the same amount of active principle. The larger dose of phenarsine hydrochloride (0.068 Gm.) yields 0.047 Gm. of 3-amino-4-hydroxyphenylarsenoxide. This corresponds to 0.06 Gm. of mapharsen content of the active principle. Both phenarsine hydrochloride and mapharsen contain about 25 per cent trivalent arsenic.

Dichlorophenarsine hydrochloride in the dry form does not contain arsenoxide. This is of importance because this drug is more stable. Arsenoxide is formed by the chemical reaction which takes places in the ampule when distilled water is added to the drug. Mapharsen, which is arsenoxide hydrochloride hemialcoholate, becomes arsenoxide on the addition of water. The structural formulas are given for both reactions.

Toxicity tests were carried out according to the standard National Institute of Health procedures, with the following results:

> Of 77 rats receiving 15 mg. per kilogram intravenously the percentage of survivals was 96; of 62 rats receiving 16 mg. per kilogram the percentage surviving was 85.5; of 74 rats receiving 18 mg. per kilogram the percentage was 71; of 18 rats receiving 22 mg. per kilogram the percentage was 61. The toxicity of phenarsine hydrochloride does not differ materially from that of the mapharsen.

Therapeutic activity was determined by curative tests on rats infected with Trypanosoma equiperdum:

> Of infected animals treated with 0.375 mg. per kilogram of phenarsine hydrochloride, 30 per cent survived the 28 day observation period; of those receiving 0.4375 mg. per kilogram, 24 per cent; of those receiving 0.500 mg. per kilogram, 41 per cent, and of those receiving 0.625 mg. per kilogram, 61 per cent.
>
> These results do not differ materially from those obtained with mapharsen.

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96. Long, W. E.: Treatment of Syphilis with Phenarsine Hydrochloride: Preliminary Report, Arch. Dermat. & Syph. **47**:226 (Feb.) 1943.

97. Guy, W. H.; Goldmann, B. A., and Gannon, G. P.: Phenarsine Hydrochloride in the Treatment of Syphilis: Preliminary Report, Arch. Dermat. & Syph. **47**:235 (Feb.) 1943.

The therapeutic index of both dichlorophenarsine hydrochloride and mapharsen is essentially the same, about 28.

From January 1941 to July 1942, 233 patients were given 2,581 intravenous injections of dichlorophenarsine hydrochloride. In 4 patients with primary syphilis who were hospitalized for dark field studies, spirochetes disappeared from the lesions within twenty-four hours. Cutaneous lesions cleared rapidly, and in the majority of cases they had disappeared entirely in an average of fourteen days. No serious late reactions were encountered. A small percentage of the patients had mild symptoms, of nausea, vomiting, slight headache or pain in the arm, when the drug was administered slowly.

Clarification is desirable as to the confusion between mapharsen and dichlorophenarsine hydrochloride.

Mapharsen is the hemialcoholate of 3-amino-4-hydroxyphenylarsine oxide hydrochloride,

$-NH_2.HCl$. A solution of the corresponding dichloroarsine,

$NH_2.HCl$, was made commercially available by May and Baker under the trade name halarsol some twelve years ago, before the development of mapharsen. The nonproprietary name dichlorophenarsine hydrochloride has been proposed for this compound for inclusion in the first supplement to the United States Pharmacopeia XII. The Squibb preparation clorarsen and the Winthrop preparation phenarsine-Winthrop consist of this dichloroarsine packaged as dry powder with enough alkali to make a neutral solution.

Electrometric titrations on several dichloroarsines, including the Squibb product, show that when a solution of the dichloroarsine is brought up to p_H 5 it is converted quantitatively to the arsine oxide. In other words, a solution of the dichloroarsine at p_H 5 to 7, such as would be used therapeutically, is chemically identical with a solution of mapharsen. Provided only that the drugs are used in equimolar amounts, they must give therapeutically the same result. Data on toxicity in vivo and on spirocheticidal activity in vitro have proved this to be the case. Moreover, since the dichloroarsine has the same toxicity and treponemicidal activity, whether neutralized with sodium hydroxide, sodium carbonate or sodium citrate, it seems clear that the nature of the base used has no demonstrable effect on the biologic activity of the resultant arsine oxide.

From the point of view of therapeutic activity, the several preparations are therefore identical. Dichloroarsines in general are more stable than the corresponding arsine oxides. To that extent an ampule containing the dry dichloroarsine, with enough dry alkali to make a neutral solution on the addition of water, might be more stable than an ampule of mapharsen; and the undesirable chemical changes sometimes noted in mapharsen ampules, evidenced by the discoloration of the powder, and believed to be due to oxidation of the aminophenol grouping, might thus be avoided or minimized.

Trisodarsen.—Trisodarsen (trisodium arsphenamine sulfate) is the trisodium salt of 3,3′ diamino 4,4′ dihydroxyarsenobenzene N,N′ di-methylene sulfonic acid. Over a period of eight years, a total of 6,852 injections of this drug has been given at the University of Pennsylvania Hospital. A resume of this experience is reported by Beerman, Pariser, and Gordon.[98] This study covers a total of 550 patients with syphilis. Of these, 234 had latent syphilis, 15 had late syphilis, 7 had congenital infections and 291 were in the early stages of the disease.

Under treatment with trisodarsen, lesions of early syphilis were found to heal rapidly, S. pallida disappearing in less than ninety-six hours. Forty-four per cent of the patients had untoward reactions to the drug. Of the severe reactions, there were 7 cases of exfoliative dermatitis, 4 cases of purpura, 5 of bleeding from the nose or mouth and 2 instances of aplastic anemia. The serologic response to treatment compared favorably with other trivalent arsenicals, and the number of clinical or serologic relapses was not unduly large. In spite of the high incidence of serious reactions, the drug is considered "promising" by the authors.

Bismarsen.—A review of fourteen years' experience with the use of bismarsen (bismuth arsphenamine sulfanate) at the University of Pennsylvania is presented by Beerman, Shaffer and Livingood.[99] In this study, 823 patients received a total of 18,286 injections of bismarsen. Of these patients, 299 had latent and seroresistant syphilis, 151 had prenatal syphilis, 57 had late cutaneous or osseous involvement, 117 were in the early stages of the disease, 101 had cardiovascular involvement and 98 had syphilis of the central nervous system. Bismarsen was administered whenever possible twice a week and in uninterrupted courses of sixty injections or more.

The drug was found to be relatively nontoxic and easily administered. Although it was frequently used to treat patients who had shown untoward reactions to other arsenicals, the incidence of local and systemic reactions was low, only 5 cases of dermatitis and 5 of purpura having been observed. There were no fatalities.

In cases of early syphilis, bismarsen brought about healing, although more slowly than did other arsenicals. The spirocheticidal action was also more gradual. It was shown to be effective in preventing progression, relapse and late complications. In cases of latent syphilis, reversal of serologic reactions was accomplished and progression of the disease prevented. With cardiovascular, late congenital and benign late forms of syphilis, favorable results were attained. The action of bismarsen was considered too slow for the treatment of active interstitial keratitis. In cases of neurosyphilis the drug is useful only for patients for whom fever and other forms of chemotherapy are contraindicated.

New Arsonic Acids.—Several new arsonic acids, derived from naphthalene and biphenyl, have been prepared by Doak and his co-workers [100] in order that their spirocheticidal activity might be investigated. The arsonic acids have been reduced to the corresponding arsine oxides.

Mapharsen.—Fractional dose therapy of experimental trypanosomiasis has shown the trypanocidal action of mapharsen in vivo to be of relatively short duration. Yet arsenic can be recovered from the blood and tissues of the experimental

98. Beerman, H.; Pariser, H., and Gordon, J. H.: Further Observations on Trisodarsen for the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:670 (Nov.) 1942.

99. Beerman, H.; Shaffer, B., and Livingood, C. S.: Bismarsen (Bismuth Arsphenamine Sulfonate) for the Treatment of Syphilis, J. A. M. A. **120**:333 (Oct. 3) 1942.

100. Doak, G. O.; Eagle, H., and Steinman, H. G.: Arsine Oxides of Naphthalene and Biphenyl, J. Am. Chem. Soc. **64**:1064 (May) 1942.

animal for relatively long periods after injections of mapharsen. Wright and Peters [101] have studied experimentally the apparent lack of parallelism between these two facts.

The procedure consisted in determining the minimum trypanocidal concentration of the blood arsenic of rats at various intervals after intravenous injection of the maximum tolerated dose of mapharsen and comparing this with the minimum trypanocidal concentration of the uninjected drug. Following the injection of mapharsen, the trypanocidal activity of the blood was exceedingly high for one-half to one hour, but decreased steadily thereafter and disappeared completely after twenty-four to thirty-six hours. Blood arsenic levels dropped slowly but became somewhat higher as arsenic was returned to the blood stream from the tissues. Since this returning arsenic is nontrypanocidal and since the incubation of mapharsen with blood produces a much slower decrease in activity than that occurring in vivo, it appears that the tissues play a major role in inactivation of the drug.

Despite the fact that the present day treatment of syphilis calls for repeated administration of subcurative doses of arsenical drugs in alternate courses with bismuth, most studies of the curative effects of antisyphilitic drugs in experimental animals have been made on the basis of the injection of a single completely curative dose. To ascertain the therapeutic effects of subcurative doses, Swinyard, Hirschfelder and Wright [102] have studied the results of serial administration of various subcurative doses of mapharsen in the treatment of T. equiperdum infections in rats.

From the standpoint of the effect of dosage, there appeared to be a comparatively sharp break in the efficiency of doses smaller than 50 per cent of the minimal curative dose. Doses in excess of this were uniformly curative in two or more doses at all time intervals, even at intervals of ninety-six hours, apparently because the initial dose destroyed a sufficiently large number of the organisms that the infection could not be restored to its former level by the time the next injection was given.

At dosages below 50 per cent of the minimal curative dose, the results were much more dependent on the time interval between injections. With smaller doses, the duration of the durative efficiency of a single injection of mapharsen in the rat did not exceed twelve hours.

The authors' results indicate:

> . . . that the duration of the trypanocidal action of mapharsen is sufficiently short that maximum clinical benefit cannot be expected to be obtained from the injection of the drug at weekly or even semi-weekly time intervals. Maximum therapeutic results from the clinical use of mapharsen appear to be indicated by . . . the administration of repeated subcurative doses of the drug at a time interval sufficiently short that a constantly spirocheticidal concentration of the drug will be maintained in the blood stream night and day for a period of time sufficiently long to produce a high percentage of "permanent cures" in a single course of treatment. The time interval elapsing between injections should apparently not exceed 12 hours. The dosage should be the maximum that the incidence of clinical toxicity will permit. . . . The injection of dosages that are too small, even though injected at frequent intervals, may be comparatively wasteful therapeutically from failure to achieve the necessary minimal curative blood level of the arsenic compound, yet potentially dangerous from the standpoint of the production of toxic manifestations.

101. Wright, H. N., and Peters, L.: Trypanocidal Activity and Arsenic Content of Rat Blood Following Intravenous Administration of Mapharsen, Proc. Soc. Exper. Biol. & Med. **52**:3 (Jan.) 1943.

102. Swinyard, E. A.; Hirschfelder, A. D., and Wright, H. N.: The Therapeutic Effects of Repeated Subcurative Doses of Mapharsen on T. Equiperdum Infections in the Rat, J. Pharmacol. & Exper. Therap. **75**:367 (July) 1942.

Trivalent arsenicals of the arsphenamine series are poorly absorbed from the gastrointestinal tract and have little therapeutic activity when administered by mouth. This is largely due to the fact that arsphenamines behave somewhat as colloids, and arsphenamine itself is largely insoluble at the p_H of the body fluids.

Because mapharsen is soluble and freely dialyzable at neutrality, Rosenthal [103] has tested its therapeutic efficacy orally against T. equiperdum infections in mice. Since it was anticipated that the arsenoxides would cause local irritation of the gastrointestinal tract, further experiments were conducted in which glutathione was added to the mapharsen solution prior to administration.

Thus administered orally, mapharsen was found to possess curative action against T. equiperdum infections in mice. The addition of 2 mols of glutathione decreased toxicity without affecting therapeutic activity.

Effectiveness of Arsenicals Against Bacteria.—Osgood and his co-workers [104] have determined in cultures of living human marrow cells the comparative effectiveness of several arsenical and sulfonamide drugs against various species of bacteria. Clinically and in experimentation on animals, variables such as the size of the inoculum, the number and strain of organisms present, the natural resistance of the host and the presence of antibodies are difficult to control. By using cultures of human marrow, these variables can be controlled, quantitative studies thus being made more reliable.

In marrow cultures, arsenic trioxide and seven pentavalent organic arsenicals tested were ineffectual against all the species of bacteria studied. Six trivalent arsenicals (neoarsphenamine, arsphenamine, sulfarsphenamine, trisodarsen, marpharsen and phenarsine hydrochloride), in concentrations corresponding to about 100 micrograms of arsenic per hundred cubic centimeters, were effective against six species of bacteria: Staphylococcus aureus, Streptococcus viridans (groups A and B), Streptococcus haemolyticus, Corynebacterium diphtheriae, Neisseria gonorrhoeae and Haemophilus influenzae. They were ineffective against Diplococcus pneumoniae, Escherichia coli, Eberthella typhosa, Salmonella schottmuelleri, Streptococcus viridans (group C) and Streptococcus anhaemolyticus.

"Sulfonamide Effect" of Sodium Arsanilate.—Paraaminobenzoic acid is an essential growth factor required for the multiplication of many different bacteria. The efficacy of the sulfonamide group of drugs has been explained by their structural similarity to paraaminobenzoic acid and their ability to displace this essential metabolite. Hirsch [105] points out that other substances, devoid of sulfonamide groups, may have a similar action. He notes that sodium arsanilate (sodium salt of paraaminobenzene arsinic acid) reduces the speed of bacterial growth against Bacillus coli and that the antibacterial effect of the drug can be inhibited by paraaminobenzoic acid.

Detoxication of Arsenicals with Paraaminobenzoic Acid.—Sandground and Hamilton [106] find that paraaminobenzoic acid is highly effective in reducing

103. Rosenthal, S. M.: The Trypanocidal Action of 3-Amino-4-Hydroxyphenyl Arsenious Oxide ("Mapharsen") Administered Orally with Glutathione, J. Pharmacol. & Exper. Therap. **76**:358 (Dec.) 1942.

104. Osgood, E. E., and others: The Comparative Effectiveness of Arsenical Compounds and Sulfonamide Drugs Against Bacterial Infections, J. Lab. & Clin. Med. **28**:953 (May) 1943.

105. Hirsch, J.: The "Sulfanilamide Effect" of Substances Devoid of Sulfo Groups, Science **96**:139 (Aug. 7) 1942.

106. Sandground, J. H., and Hamilton, C. R.: Studies on the Detoxication of Organic Arsenical Compounds: I. Detoxication by Means of p-Aminobenzoic Acid of Certain Pentavalent Arsenical Drugs Given in Massive Doses to Rats, J. Pharmacol. & Exper. Therap. **78**:109 (June) 1943.

fatalities among rats to which acutely poisonous doses of carbarsone, acetarsone, tryparsamide, arsanilic acid and phenylarsonic acid have been administered. This detoxication is independent of the route by which either the phenylarsonic compound or the paraaminobenzoic acid is given. There was, however, no inhibition by paraaminobenzoic acid of the trypanocidal action of these pentavalent arsenical drugs.

The same authors [107] found it difficult to determine what quantitative relationship exists between the minimal amount of paraaminobenzoate required to neutralize the action of any specified quantity of pentavalent arsenical. By the administration of sufficient paraaminobenzoate, practically all rats were protected against a dose of pentavalent arsenicals sufficient to kill all the animals. It was found that 15 mg. per kilogram of paraaminobenzoate was sufficient to protect 50 per cent of the rats and to prolong the survival time of a group of rats receiving 400 mg. per kilogram of arsanilic acid.

Continuing the study, Sandground [108] found that the time factor entering into the sequence of administering uniform doses of paraaminobenzoate and either of two typical phenylarsonic acid derivatives to rats is sufficient to influence the survival rate of the group. Injection of paraaminobenzoate up to three hours before the administration of the arsenical confers protection on nearly all animals. In contrast, the injection of the arsenical thirty minutes before the giving of the paraaminobenzoate is associated with a reduction in the group protection, and this reduction is in direct proportion to the increase in the time interval.

Similarity of Bismuth Preparations.—According to Clausen and his co-workers,[109] there exists a striking qualitative and quantitative similarity of toxicities and limits of tolerance as well as of antisyphilitic efficacy among the various bismuth preparations when they are administered intravenously. When they are given intramuscularly, the spirocheticidal activity does not differ significantly from that following intravenous administration, although the tolerance of the host is markedly increased.

The similarity of the maximal tolerated dose and the therapeutic indexes of the compounds tested when given intravenously, in contrast to their marked differences when given intramuscularly, indicates that the difference in rate of absorption from intramuscular deposits is the most important factor in accounting for any variation which occurs.

The therapeutic efficacy of a bismuth compound, as well as its toxicity, is in direct proportion to its content of elemental bismuth. The similarity of the minimal curative dose of any bismuth preparation administered either intravenously or intramuscularly and the similarity in the toxicity of preparations given intravenously suggest that basically all bismuth compounds ultimately act in a common form rather than in the form in which they were injected.

Determinations of Blood Bismuth.—Studies of the pharmacology of bismuth compounds have not in the past included determinations of bismuth levels in the blood, which have been estimated from bismuth excreted in the urine.

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107. Sandground, J. H., and Hamilton, C. R.: Studies on the Detoxication of Arsenical Compounds: II. Correlation of the Quantity of p-Aminobenzoic Acid Required to Protect Rats Against High Doses of Carbarsone and Arsanilic Acid, J. Pharmacol. & Exper. Therap. **78**:203 (June) 1943.

108. Sandground, J. H.: Studies on the Detoxication of Arsenical Compounds: III. The Time Factor Influencing p-Aminobenzoate Protection of Rats Receiving Lethal Doses of Phenyl Arsonates, J. Pharmacol. & Exper. Therap. **78**:209 (June) 1943.

109. Clausen, N. M.; Longley, B. J.; Green, R. E., and Tatum, A. L.: A Study of the Similarities of Several Representative Types of Bismuth Preparations Used in the Therapy of Experimental Syphilis, J. Pharmacol. & Exper. Therap. **76**:338 (Dec.) 1942.

Delp, Walker and Sondern[110] have succeeded in making determinations of blood bismuth on 7 syphilitic patients receiving a water-soluble bismuth compound (potassium bismuth saccharate). Values of 3 to 5 micrograms were obtained promptly after the intramuscular injection of this preparation. Cumulative effects were evident with multiple injections, and values of 5 to 7 micrograms were easily maintained. After cessation of therapy there was evidently a rapid fall in blood bismuth levels, but minimal amounts of the metal were found for a considerable time.

Bismuth Melanosis and Female Sex Hormones.—Sulman and his co-workers[111] found that when female albino rats were simultaneously treated with organic bismuth compounds (bismuth phenylethylacetate, bismuth butylthiolaurate, bismuth chinolinate and bismuth adipinate) and estrogens or chorionic gonadotropin, bismuth melanosis of the vagina developed in 30 to 80 per cent of the animals. The reaction seemed to be conditioned by hyperemia of the vagina from the action of the hormones. Bismuth melanosis in sexual organs other than the vagina was seldom observed, and the rest of the body was always found free of impregnation with bismuth. In male rats simultaneously treated with a bismuth compound and testosterone propionate, bismuth melanosis of the genital tract occurred only occasionally.

Iodine in Saliva.—Bruger and Member[112] have found marked increases in the concentration of iodine in the saliva following the oral administration of potassium iodide, iodine dissolved in poppyseed oil and ethyl diiodobrassidate. The maximal concentration of salivary iodine occurred approximately one to two and a half hours after the ingestion of potassium iodide.

TREATMENT

Bismuth Compound for Latent Syphilis.—Kahn and Becker[113] report the results of treatment of 200 patients with late latent syphilis with "large amounts of bismuth combined with a moderate amount of an arsenical," comparing them with the results obtained by the Cooperative Clinical Group. The scheme of therapy used was as follows: one course of ten injections of a bismuth compound; three courses of combined bismuth and arsenical treatment, after each of which was interposed one month's rest and a course of eight injections of a bismuth compound; another rest period, and finally three long courses of bismuth therapy separated by six months and one year. Total therapy amounted to twenty-four doses of an arsenical and eighty-six of a bismuth compound. For this type of treatment, the authors claim an advantage over the shorter, alternate course scheme of therapy used by the Cooperative Clinical Group, who obtained maximum results with twenty injections of an arsenical and less bismuth than was used by the authors.

The data presented, however, do not support the authors' premise, since the material has been analyzed with insufficient regard for the statistical concepts involved. The two groups of patients are not strictly comparable. In the first

110. Delp, M. H.; Walker, N., and Sondern, C. W.: Blood Bismuth Studies: Preliminary Report of Syphilitic Patients Treated with a Water-Soluble Preparation, Am. J. Syph., Gonor. & Ven. Dis. **27**:193 (March) 1943.

111. Sulman, F.; Levy-Hochman, S., and Tietz, H. G.: Selective Bismuth Melanosis of the Female Genital Tract Induced by Treatment with Sex Hormones, Endocrinology **32**:293 (March) 1943.

112. Bruger, M., and Member, S.: On the Excretion of Iodine in the Saliva, Am. J. Physiol. **139**:212 (June) 1943.

113. Kahn, D., and Becker, S. W.: The Use of Bismuth Compounds in Syphilotherapy: II. The Results of Treatment of Latent Syphilis by Bismuth Compounds Combined in Part with Arsenicals, J. A. M. A. **120**:338 (Oct. 3) 1942.

place, it is necessary to realize that of the patients in the Cooperative Clinical Group series who received prolonged treatment, many were so treated because of need for further therapy. In the present study, prolonged treatment was given routinely. In addition, the previous treatment which the patients in the present group received was disregarded, despite the fact that 30 per cent had received such therapy. Moreover, all of the patients in the present group had syphilis in the later stage of latency, whereas 30 per cent of the Cooperative Clinical Group series had early latent infection.

The higher proportion of satisfactory results in the authors' series is more apparent than real. The percentage of patients with clinical progression, the true test of therapy of late latent syphilis, is smaller in their group among patients under observation up to ten years; but among those observed more than ten years a smaller percentage of the Cooperative Clinical Group's series had progressed. For an unexplained reason, none of the patients in the authors' group had died, and none was "under treatment, doing well." A readjustment of the rates in the Cooperative Clinical Group's series in consideration of these facts improves the comparative results, bringing the observed differences within the range or chance variation.

There is no satisfactory proof that the prolongation of therapy with additional courses of bismuth improves the prognosis for patients with late latent syphilis. There is, on the other hand, reason to believe that the prevention of clinical progression can be effected satisfactorily by considerable less treatment than that indicated by Kahn and Becker.

Thiamine Hydrochloride for Lightning Pains.—Cochems and Kemp [114] treated 26 patients with typical tabetic lightning pains with thiamine hydrochloride given intravenously. The average number of injections was eighteen, with an average dose of 61 mg., over a period averaging eight months. Analysis of the results reveals that 17 patients (65 per cent) experienced no ultimate relief of pain; 4 (16 per cent) apparently obtained partial relief, and 5 (19 per cent) apparently obtained complete relief. Definite proof was lacking that improvement in any instance was due to thiamine because the observation period was insufficiently long for the exclusion of spontaneous remission and psychic effect. The authors conclude that intravenous injections of thiamine hydrochloride are valueless in the alleviation of tabetic lightning pains in the majority of cases and of doubtful value in the remainder.

Vitamin Therapy.—None of the manifestations of syphilis respond dramatically to vitamin therapy. Moreover, there is no satisfactory evidence that any of the vitamins significantly decrease the toxicity of the arsenical drugs. O'Leary [115] notes that although thiamine has been used as supplementary therapy for tabes dorsalis, lightning pains, visceral crises, atrophy of the optic nerve and interstitial keratitis and as an adjunct to tryparsamide treatment, though ascorbic acid has been used to prevent arsenical dermatitis and though riboflavin has been employed for interstitial keratitis, all have been found to have insignificant value.

UNTOWARD EFFECTS OF TREATMENT

Mortality Data.—For the past seventeen years, medical officers of the Navy have been required to submit reports of the number of doses of arsenicals administered and detailed information regarding any toxic reaction therefrom.

114. Cochems, K. D., and Kemp, J. E.: Intravenous Thiamin Chloride (Vitamin B_1) in the Treatment of Tabetic Lightning Pains, Am. J. Syph., Gonor. & Ven. Dis. **26**:574 (Sept.) 1942.

115. O'Leary, P. A.: Vitamin Therapy in Dermatology and Syphilology, Arch. Dermat & Syph. **46**:628 (Nov.) 1942.

The most recent data thus obtained have been compiled by Stephenson, Chambers and Anderson.[116] In the period 1925 to 1941, 1,792,383 injections of various arsenicals have been given, with 52 fatal reactions, a ratio of 1 death to every 34,469 injections. Fifty of the 52 deaths were due to neoarsphenamine, 1 to arsphenamine and 1 to mapharsen. A total of 288,585 injections of mapharsen have been given. The one fatality following this drug occurred twenty-four hours after the first injection. Postmortem observations included cerebral edema and hemorrhage. Of 881 reactions from all arsenicals recorded, 353 were ascribed to vasomotor phenomena and 336 to arsenical dermatitis.

Arsenical Encephalopathy.—The severe and usually fatal cerebral manifestations due to the toxic effects of arsenicals are most commonly referred to as "hemorrhagic encephalitis," although other terms have been used, such as cerebral purpura, serous apoplexy, medullary perivascular necrosis and pericapillary encephalorrhagia.

Two instances of arsenical encephalopathy following neoarsphenamine are reported by Tuta and Stagman,[117] who believe that a relationship exists between the relatively mild vasomotor or nitritoid crises and the progressive vascular changes leading to cerebral edema followed by hemorrhagic infiltrations. The most common clinical findings in the latter condition are headache, vomiting, rapid development of unconsciousness, convulsions and fever. These symptoms usually appear two or three days after the first, second or third injection of an arsenical drug. Occasionally, however, the symptoms may be delayed, and at times many injections may precede the onset. The majority of patients die within four days after the appearance of the reaction.

The authors' conception of the pathogenesis of arsenical encephalopathy is as follows:

> Vasodilatation with increased capillary permeability is followed by stasis and exudation of fluid from the terminal blood vessels causing a cerebral edema. Instances have been reported where the cerebral edema has been a predominant feature and only a few or no hemorrhages were found. Later, red blood cells escape from the walls of the capillaries and vessels of precapillary dimensions, resulting in the picture of a hemorrhagic encephalitis with clinical symptoms, particularly of stupor or coma.

As Halcrow[118] points out, the causal factor in arsenical encephalopathy is unknown, but it seems to be unrelated to the arsenic radical, since poisoning with inorganic arsenic compounds does not give rise to such cerebral symptoms. The authors think it unlikely that overdosage is at fault, since in most recorded cases symptoms have occurred after the second or third injection. However, in view of the greatly increased frequency of the reaction during and after the intensive arsenotherapy of early syphilis, dosage is surely incriminated. It is not in the nature of a Herxheimer reaction since cerebral complications have followed arsenical therapy in nonsyphilitic patients. As symptoms occur early in the course of therapy, it is possible that an allergic factor exists. There is evidence of a toxic action of the drugs on capillaries.

Attention is drawn to the need for early recognition of the condition, since therapy seems unavailing unless instituted soon after the onset.

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116. Stephenson, C. S.; Chambers, W. M., and Anderson, L. T.: (*a*) Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1941, U. S. Nav. M. Bull. **40**:1015 (Nov.) 1942; (*b*) Toxic Effects of Arsenical Compounds as Employed in the Treatment of Disease in the United States Navy, 1941, ibid. **41**:259 (Jan.) 1943.

117. Tuta, J. A., and Stagman, J.: Encephalopathy Following Neoarsphenamine, Am. J. Clin. Path. **12**:387 (July) 1942.

118. Halcrow, J. P. A.: A Case of Haemorrhagic Encephalopathy Following Arsenical Therapy, Brit. M. J. **1**:663 (May 29) 1943.

Having observed 4 patients with arsenical encephalopathy, 3 of whom were pregnant women, Nelson and his co-workers [119] believe the condition to be more frequent than usually is stated. In 3 instances hemorrhagic encephalitis occurred about the tenth day after treatment was begun with sodium arsphenamine or mapharside. All the reactions occurred in the winter season, at a time when vitamin intake is relatively low. It is impossible to determine in advance which patient will have this complication, but the authors' experience suggests that a pregnant woman should be regarded as a "potential reactor."

Courville and Marsh,[120] who have studied 12 cases of postarsphenamine encephalopathy, describe multiple symmetric foci of hemorrhagic necrosis as part of the pathologic picture of this condition. According to these authors, the lesion is closely allied to pericapillary encephalorrhagia, in that it is composed of many perivascular ring hemorrhages. There was a tendency for these hemorrhagic foci to localize in regions of both gray and white matter of the brain. The corpus callosum, the optic thalami, the external capsule and the frontal and parieto-occipital centrums were the sites of predilection. There was also a tendency for the lesion to occur in symmetric areas of the brain.

From the data presented, it is apparent that multiple symmetric foci of hemorrhagic necrosis, together with the disseminated petechial hemorrhages and possible gross cerebral hemorrhage, constitute the essential pathologic changes in the clinical syndrome of postarsphenamine hemorrhagic encephalopathy.

In Thomas, Wexler and Dattner's [121] series of 764 patients treated for early syphilis with massive dosages of mapharsen, there were 8 patients with symptomatic cerebral reactions, 2 of whom died. In their experience, arsenical reactions of this type vary as to time of onset in relation to treatment and as to duration of symptoms. The significant observation is recorded that in patients with cerebral reactions there is usually a marked increase in protein in the cerebrospinal fluid. This is usually but not necessarily associated with pleocytosis.

Because of the authors' fear of cerebral reactions, the spinal fluid was examined before and after intensive treatment in 250 cases of early syphilis. The spinal fluid was also examined whenever "secondary" fever or unusual symptoms indicated it. In the course of these examinations, 8 patients were found who had marked abnormalities of the spinal fluid but no symptoms. It is believed that these alterations may portend serious trouble and that their finding calls for interruption of therapy.

Arsenical Myelopathy.—Arsenical intoxication may produce pathologic changes in an organ in two ways: by direct action on the parenchyma and by affecting its nutrition through involvement of the nutrient blood vessels. In the brain, the lesions of arsenical toxicity usually are of the vascular type, producing the classic picture of "hemorrhagic encephalitis."

Lichtenstein [122] notes that, in contrast to the changes in the brain, the changes in the spinal cord following therapy with the arsenicals usually results from damage to the parenchyma. Histologic alterations of postarsphenamine myelitis

119. Nelson, R. B.; McGibbon, C., and Glyn-Hughes, F.: Arsenical Encephalopathy: A Complication Occurring During the Treatment of Syphilis, Brit. M. J. **1**:661 (May 29) 1943.

120. Courville, C. B., and Marsh, C.: Cerebral Lesions Following Administration of Neoarsphenamine: Multiple Symmetric Foci of Hemorrhagic Necrosis of the Brain, Arch. Dermat. & Syph. **46**:512 (Oct.) 1942.

121. Thomas, E. W.; Wexler, G., and Dattner, B.: Cerebral Reactions Associated with Massive Mapharsen Treatment of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:529 (Sept.) 1942.

122. Lichtenstein, B. W.: Acute and Subacute Toxic Myelopathies Following Therapy with Arsphenamine, Arch. Neurol. & Psychiat. **48**:740 (Nov.) 1942.

include: degeneration of the ganglion cells and the myelin of the nerve fibers, with proliferative changes in the astroglia; malacia; necrosis, and inflammatory phenomena, such as perivascular and leptomeningeal cellular infiltrations.

As a rule, postarsphenamine myelopathy is located in the lower thoracic and the lumbar portion of the spinal cord, although the parenchymatous alterations may extend upward into the brain stem. Degeneration of the peripheral nerves not infrequently is associated with the lesions of the cord. The disorder usually is acute or subacute in course, with death resulting from respiratory paralysis or sepsis. In nonfatal cases there is evidence of permanent damage to the spinal cord.

The Bone Marrow During Intensive Arsenotherapy.—Studying the sternal bone marrow of 14 patients during intensive arsenotherapy (five day intravenous drip), Schwind [123] found no significant effect of the treatment on either the erythrocytic or the leukocytic series of cells. Three of the patients had a shift to the left in the Schilling index of the peripheral blood, although the total leukocyte count was within normal limits. These patients had a corresponding increase in neutrophilic band forms and metamyelocytes in the bone marrow. The other 11 had normal peripheral blood pictures, and the differential counts of their marrows were within the range of normal.

Histamine Treatment of Exfoliative Dermatitis.—Encouraging results from the use of histamine therapy in certain allergic conditions led Jenkins [124] to study this drug in the treatment of postarsenical dermatitis. The author believes that histamine therapy hastens recovery in this condition, since in his hands more satisfactory results were obtained than with any other type of treatment. His series of cases is small, and the interpretation of the results is complicated by the fact that some had received routine therapy with colloidal baths, ephedrine and phenobarbital. Moreover, the results were appraised on the basis of duration of hospitalization, an end point subject to considerable discretionary bias. The findings are suggestive, but further clinical trial with histamine is necessary to evaluate the proper place of this form of therapy in the treatment of exfoliative dermatitis caused by the arsenical drugs.

Sodium Thiosulfate Treatment of Exfoliative Dermatitis.—Abramowitz and his co-workers [125] report the results of treatment with sodium thiosulfate of 5 patients with arsenical dermatitis, of 1 with dermatitis due to bismuth and of 1 with dermatitis due to gold. All patients were put on a restricted diet, usually bananas and milk. Determinations of arsenic in the urine were made, and freshly prepared sodium thiosulfate was administered intravenously. The authors conclude:

1. Using as a criterion the twenty-four hour output of arsenic, we have been unable to demonstrate that sodium thiosulfate in the doses commonly employed increases the urinary excretion or alleviates dermatitis due to the arsphenamines. It is therefore of little diagnostic or therapeutic value.

2. Although our experimental evidence is limited, it would appear that sodium thiosulfate is without effect on urinary excretion of bismuth or on dermatoses subsequent to alternate bismuth and arsenic therapy. In 1 case the urinary excretion of gold also was not affected by sodium thiosulfate.

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123. Schwind, J. L.: The Bone Marrow in the Five Day Treatment of Syphilis, Proc. Soc. Exper. Biol. & Med. **52**:128 (Feb.) 1942.

124. Jenkins, E. C.: Treatment of Postarsenical Dermatitis with Histamine, Ven. Dis. Inform. **24**:11 (Jan.) 1943.

125. Abramowitz, E. W.; Mattice, M. R., and Botvinick, I.: Doubtful Value of Sodium Thiosulfate in Therapy of Arsenical Dermatitis, Arch. Dermat. & Syph. **47**:175 (Feb.) 1943.

Postarsphenamine Jaundice.—In a twelve month study of icterus in the Canadian Army, Mitchell [126] compares the incidence of catarrhal jaundice with the occurrence of jaundice following arsenotherapy of syphilis.

The incidence of clinical jaundice among those receiving arsenotherapy for syphilis was 36.5 times as high as in those who were not so treated. The drug used for about 90 per cent of the men was neoarsphenamine. Jaundice was three times as frequent in this group as in the smaller group treated with mapharsen. It is suggested, although without documentation, that there is a large number of cases of infectious hepatitis without jaundice and that it is the association of two hepatotoxic agents, the arsenic and the toxic agent of infectious hepatitis, which produces a higher incidence of infectious hepatitis in patients under arsenotherapy.

Respiratory Allergy to Arsenicals.—Cutaneous hypersensitivity to the arsenical drugs used in the treatment of syphilis is not unusual. Respiratory hypersensitivity, however, is sufficiently rare as to warrant single case reports. Saunders [127] reports an instance of such allergy, in which sneezing, rhinorrhea and asthma followed the inhalation of mapharsen, arsphenamine or neoarsphenamine. Similar symptoms followed the making of patch tests or scratch tests with these same drugs.

Erythema of the Ninth Day.—Gresser and Thomas [128] report that superficial punctate keratitis may occur in association with fever and a generalized erythema of the skin as part of the clinical entity known as Milian's erythema of the ninth day. The complication occurred in 2 syphilitic patients and in a patient with Vincent's infection after treatment with trivalent arsenicals. The immediate complaints consisted of smoky or blurred vision, accompanied by redness of the eyes, photophobia, lacrimation and a mild sensation of sandiness or of a foreign body. These symptoms either followed the height of the erythema or occurred as the erythema faded and desquamated. The acute stage persisted from two to four weeks. The punctate lesions, which by slit lamp examination appeared to be edematous cells rather than erosions, tended to appear in crops at five to six day intervals, the new lesions appearing before resolution of the old, and affected mainly the central corneal area. In all cases the keratitis was self limited, being uninfluenced in evolution by therapy.

Bismuth Stomatitis.—Ronchese [129] reports favorable results from the use of hexametaphosphate and talc in the form of a tooth powder in the treatment of bismuth stomatitis.

Bismuth Anuria.—The toxic effects of bismuth on the kidney ordinarily are benign. However, Witkowski [130] reports 2 cases of severe renal damage in infants under treatment with bismuth for congenital syphilis. In 1 anuria and death followed the administration of ten injections of sodium bismuth thioglycollate.

Stitt [131] reports severe renal damage following a single dose of sodium bismuth thioglycollate to an infant, and cautions that care should be exercised in administering bismuth, especially to infants.

126. Mitchell, H. S.: The Incidence of Catarrhal Jaundice Compared with Jaundice Following Arsenotherapy of Syphilis, Canad. M. A. J. **48**:94 (Feb.) 1943.

127. Saunders, T. S.: Respiratory Allergy from the Arsphenamines, J. Allergy **14**:76 (Nov.) 1942.

128. Gresser, E. B., and Thomas, E. W.: Superficial Punctate Keratitis in Milian's Erythema of the Ninth Day, Arch. Ophth. **28**:245 (Aug.) 1942.

129. Ronchese, F.: Bismuth Stomatitis, Urol. & Cutan. Rev. **46**:462 (July) 1942.

130. Witkowski, J. L.: Toxic Effects with Anuria Resulting from Bismuth Injections in the Treatment of Congenital Syphilis in Infants, Urol. & Cutan. Rev. **46**:770 (Dec.) 1942.

131. Stitt, P. G.: Bismuth Poisoning: Toxic Effects with Anuria Resulting from a Single Injection of a Bismuth Preparation, Urol. & Cutan. Rev. **46**:780 (Dec.) 1942.

Embolia Cutis Bismuthica.—Arterial embolism following the injection of bismuth is a rare untoward reaction to antisyphilitic treatment. Reporting a case of embolia cutis bismuthica, Goldschlag [132] suggests that even the most careful technic may fail to prevent the accident. A small amount of bismuth may be deposited in the wall of an artery and subsequently rupture into the lumen. To prevent the accident the author advises that needles of relatively wide gage be used, that after aspiration the needle be detached and that injection be made into a muscle which is relaxed.

Bismuth Hepatitis.—When jaundice complicates the treatment of a patient with syphilis, the complication is usually attributed to intercurrent infection, to the administration of arsenicals or possibly to hepatorecurrence of syphilis. Kulchar and Reynolds [133] stress the importance of bismuth as a cause of hepatitis and report 121 cases in which the heavy metal appeared to be implicated.

In treating 1,032 inmates of San Quentin prison, the authors observed 121 who became jaundiced while bismuth was being given. Treatment had been with iodobismitol with saligenin for 82 of the 121 patients. Only 4 patients became icteric when the initial course of therapy was with bismuth. The remaining 117 had received arsenicals in some form prior to the course of bismuth therapy during which hepatitis occurred. The onset of jaundice was noted within four weeks of the last injection of an arsenical drug in 34 patients, but evidence of hepatic damage did not appear until four or more weekly injections of bismuth had been given in 83, and not until after eight or more weekly injections in 56.

Treatment was subsequently continued in 107 of the cases. In 9 there was a recurrence of the jaundice. This occurred during bismuth therapy in 4, while arsphenamine was given in another 4, and during treatment with tryparsamide in 1.

The authors believe that the effect of previously administered arsenicals as well as factors of diet, alcoholism and intercurrent infection all predispose the liver to damage from bismuth and that bismuth hepatitis is a summation effect resulting from the interaction of several factors which individually are insufficient to cause the clinical manifestations of hepatitis, with bismuth the precipitating factor. The occurrence of signs or symptoms suggestive of toxic hepatitis during antisyphilitic therapy is a relatively frequent and perplexing problem. Kulchar and Reynolds outline a fairly convincing brief to indict bismuth, but their data lend themselves also to conclusions favoring arsenical causation in many of the cases presented. Most syphilotherapists, while admitting that bismuth may precipitate toxic hepatitis in a patient with preexisting damage of the liver, question the frequency with which it does so.

EARLY SYPHILIS

Dark Field Study.—Branch [134] stresses certain pertinent observations on the diagnosis of early syphilis by dark field microscopy: (1) that clinical examination alone is unsatisfactory, since a positive result of dark field examination not infrequently is found in lesions lacking the classic features of induration, painlessness and inguinal lymphadenopathy; (2) that spirochetes other than S. pallida frequently are found in penile lesions, in some cases associated with the organism of

132. Goldschlag, F.: Embolia Cutis Bismuthica: An Untoward Accident Following the Intramuscular Administration of Bismuth Subsalicylate in Oil, M. J. Australia **2**:144 (Aug. 22) 1942.

133. Kulchar, G. V., and Reynolds, W. J.: Bismuth Hepatitis: A Survey of One Hundred and Twenty-One Cases, J. A. M. A. **120**:343 (Oct. 3) 1942.

134. Branch, A.: Darkfield Examination of Penile Lesions, Canad. M. A. J. **48**:55 (Jan.) 1943.

syphilis, and (3) that a single negative result of dark field examination does not rule out syphilis. Many experienced physicians do not concur in the author's recommendation of the delayed dark field examination as a practical procedure. Since the accurate identification of S. pallida requires observation of the organism in its motile state, and since motility rapidly is lost with the passage of time outside the body, the delayed procedure is far from being entirely satisfactory for the definitive diagnosis of syphilis.

In the diagnosis of secondary syphilis, many physicians rely on the clinical characteristics of the eruption plus a positive serologic reaction, examination for S. pallida by dark field microscopy being used only when moist papules (condylomas) are present. The feasibility of examining serum from other cutaneous lesions under the dark field microscope is championed by Agee,[135] whose case reports indicate that the procedure is practical for routine use in the clinic. The advantages of the method are that the finding of S. pallida definitely establishes the diagnosis and that treatment may be started without waiting for the report of the serologic test.

Newer Concepts of Reinfection.—Schoch and Alexander[136] point out that in patients with early syphilis treated with intensive arsenotherapy reinfection may be relatively frequent. According to their published reports, earlier workers with intensive treatment methods, recognizing the extreme difficulty of differentiating reinfection from infectious relapse, have leaned to the side of conservatism and have classified all such conditions as relapse, and therefore as indicating failure of treatment. However, the clinical evidence in favor of reinfection in many patients given intensive arsenotherapy is at least as strong as the evidence for heretofore accepted examples of reinfection in patients treated by standard methods.

Ten cases of reinfection are recorded. Dark field observations, quantitative reagin titer curves and epidemiologic data were used to support clinical observations and impressions. It is highly desirable to make the differentiation between infectious relapse and reinfection in patients treated by intensive methods, since only thus can the results of such therapy be evaluated properly.

Many attempts have been made to set up suitable criteria for differentiating infectious relapse of syphilis from reinfection. Such criteria have not been entirely satisfactory. The widespread use of intensive arsenotherapy has reopened the question and reemphasized the importance of the problem, since the criteria for patients receiving "standard" treatment are not suitable for intensively treated patients. Shaffer[137] reviews the criteria which have been proposed, suggesting the following for patients given intensive treatment:

1. Accuracy of the original diagnosis of syphilis assumed on the basis of the administration of intensive treatment by organized hospital or clinic.

2. Patient has remained seronegative or has progressed to that state.

3. Spinal fluid examination negative prior to second infection. (This is desirable but not essential.)

4. A lesion, clinically acceptable as a chancre, develops at a site different from the first.

5. Patient is seronegative but darkfield positive at time of second infection.

6. Definite exposure history for second infection. (Ideally, source of second infection should be identified.)

135. Agee, O. F.: The Use of the Darkfield Microscope for Diagnosis of Generalized Secondary Lesions of Syphilis, New Orleans M. & S. J. **95**:329 (Jan.) 1943.

136. Schoch, A. G., and Alexander, L. J.: Reinfection in Syphilis: Newer Concept of Reinfection Encountered with Ten-Day Arsenotherapy of Early Syphilis Controlled by Quantitative Serologic Tests, Am. J. Syph., Gonor. & Ven. Dis. **27**:15 (Jan.) 1943.

137. Shaffer, L. W.: Criteria of Reinfection in Syphilis, Ven. Dis. Inform. **24**:113 (April) 1943.

7. If seropositive at time of supposed second infection, patient should be held in isolation without treatment until after the proper interval, at which time secondaries develop to establish validity.

8. Seropositive cases of clinically acceptable primary lesions or cases presenting characteristic secondary manifestations with a history or remains of a chancre may be classified as probably reinfection, if they fulfill the above criteria.

Supposed reinfections occurring within 6 months after intensive treatment is completed cannot be differentiated from potential superinfections; cases occurring at a later date may be assumed to be reinfections.

INTENSIVE THERAPY

Intensive Arsenotherapy.—Evaluating the present status of intensive arsenotherapy, Shaffer [138] states:

Intensive methods of treatment must still be considered experimental. The potential hazard, at least of short intensive courses, makes it necessary to advise that they should not be attempted by physicians without extensive experience in the treatment of syphilis. Further information is being rapidly accumulated, and it is expected that such experience will permit the establishment of a definite procedure to be recommended in the near future for use in private practice and in the military services. Intensive therapy is being tried in various types of latent and late syphlis, but its use in such cases is highly experimental and not as yet recommended. Its use should be restricted to previously untreated cases of early (primary and secondary) syphilis.

Among the efforts to compress the treatment of syphilis into a period shorter than the "standard" eighteen months is the twenty week schedule studied by Hood.[139] Concomitant weekly injections of mapharsen and of a bismuth compound were given to 134 patients with early syphilis, of whom only 66 successfully completed the course of twenty weeks' treatment.

Under this schedule of treatment, 94.4 per cent of all primary and secondary lesions involuted completely within six weeks, and seronegativity was achieved by 90.9 per cent of the patients. No correlation was found between the initial reagin titer and the time required to reach seronegativity. Unsatisfactory results (seroresistance, serorelapse, clinical relapse and involvement of the central nervous system) are recorded for 13.6 per cent of the patients. The author believes that his results compare not unfavorably with the results of treatment with other arsenical drugs and other schedules of therapy.

Yeager and Connolly [140] have treated 103 patients with early syphilis by giving twenty injections of mapharsen (totaling 960 to 1,200 mg. of the drug) over a period of thirty days. In 2 of the patients toxic encephalopathy developed, and 1 died. The number of therapeutic "failures" was 9.7 per cent.

Schoch and Alexander [141] have treated 350 patients by intensive arsenotherapy. Of these, 208 were treated by the ten day syringe method (120 mg. of mapharsen per day for ten days) and 142 were given "smaller individual doses over a longer period of time." In the entire group, they encountered hemorrhagic encephalitis 3 times, with 1 death. One hundred and three patients treated by the ten day syringe method have been under observation from six to eighteen months. In this group, 77 per cent attained clinical and serologic "cure." The results in 11

138. Shaffer, L. W.: Present Status of the Intensive Arsenotherapy of Early Syphilis, Ven. Dis. Inform. **24**:108 (April) 1943.

139. Hood, B. J.: The Results of a Twenty Week Treatment Schedule for Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **27**:267 (May) 1943.

140. Yeager, F. W., and Connolly, S. M.: Short Term Intensive Arsenotherapy of Early Syphilis, Tri-State M. J. **15**:2858 (Dec.) 1942.

141. Schoch, A. G., and Alexander, L. J.: Intensive Arsenotherapy of Early Syphilis: Follow-Up Report on the Ten Day Syringe Method of Treatment, Arch. Dermat. & Syph. **46**:128 (July) 1942.

per cent are pending. In the remaining 12 per cent the treatment was a failure (3 patients with infectious relapses, 1 with periostitis, 6 with serologic relapses, and 2 with positive reactions of the cerebrospinal fluid). The authors state that "These results compare favorably with those of the 5 day continuous intravenous drip method."

Since the German invasion of Norway in April 1940, a large portion of the Norwegian Merchant Navy has been isolated from its bases but remains actively engaged in prosecution of the war. Because of the acute need for the services of the naval personnel and because of a serious increase in syphilis in this group, intensive arsenotherapy has been administered. Kvittingen[142] reports favorable results of therapy in 100 men treated by daily injections of mapharside. The first 82 patients received 760 mg. of the drug within five days; the remaining 18 received 1,000 mg. in the same period. Only 1 serious reaction is recorded, toxic encephalopathy associated with morbilliform dermatitis. Follow-up results are, for obvious reasons, difficult. It is felt that, despite the increased risk of treatment, in a time of emergency the procedure is justifiable.

Once a soldier is hospitalized for primary syphilis, he is not returned to duty until the lesion is healed. It is important, therefore to effect healing as rapidly as possible in order that the man may return to his duties and training. Pelzman and Greenwald[143] believe that by giving daily injections of mapharsen at the start of treatment the average number of noneffective days can be substantially reduced. Neoarsphenamine, because of its higher toxicity, cannot be employed in this manner.

Arsenotherapy Combined with Fever.—Thomas and Wexler[144] have administered 280 courses of intensive treatment with mapharsen alone and 549 with mapharsen combined with fever induced by typhoid vaccine. Injections of mapharsen were given twice daily (0.1 Gm. twice a day for six days). Three plans of combining fever with mapharsen were used: (1) total of 0.54 Gm. of mapharsen and four fever treatments in nine days: (2) total of 0.84 Gm. of mapharsen and two fever treatments in nine days: and (3) total of 0.7 Gm. of mapharsen and three fever treatments in seven days.

The reactions encountered with the multiple injection method were not appreciably different from, nor more frequent than, those reported with the intravenous drip method. The use of typhoid vaccine increased the discomfort of treatment but was not in itself dangerous. Two deaths are recorded (one in each of the two main treatment groups), both attributable to toxic encephalopathy.

The therapeutic results may be summarized as follows:

Treatment	Patients	Probably Favorable	Unfavorable
(1) Mapharsen (0.9-1.2 Gm.)	151	83.78%	16.22%
(2) Mapharsen (0.66-0.84 Gm.)	122	74.99%	25.01%
(3) Mapharsen (0.54-0.6 Gm.) plus 4 sessions of fever	128	86.46%	13.54%
(4) Mapharsen (0.7-0.84 Gm.) plus 2 or 3 sessions of fever	171	85.49%	14.51%

142. Kvittingen, J.: Syphilis Treated with Daily Multiple Injections of Mapharside, Brit. M. J. **1**:69 (Jan. 16) 1943.

143. Pelzman, I. A., and Greenwald, R.: Preliminary Intensive Treatment of Primary Syphilis by Daily Injections of Arsenicals, Am. J. Syph., Gonor. & Ven. Dis. **26**:627 (Sept.) 1942.

144. Thomas, E. W., and Wexler, G.: Rapid Treatment of Early Syphilis: Report of Two Hundred and Eighty Treatment Courses with Mapharsen Alone and Five Hundred and Forty-Nine Courses with Mapharsen Combined with Fever, Arch. Dermat. & Syph. **47**:553 (April) 1943.

The authors believe that their results, both with mapharsen alone (total dose 1 Gm. or more) and with a combination of fever induced with typhoid vaccine and less than 0.9 Gm. of mapharsen, compare favorably with the results of prolonged continuous routine treatment. The therapeutic results obtained with less than 1 Gm. of mapharsen alone are definitely less satisfactory than when a total dose of 1 Gm. or more is used. The risk of arsenical encephalopathy increases with the amount of mapharsen given. The combination of fever induced by typhoid vaccine with massive mapharsen therapy does not prevent cerebral reactions, but it lessens the frequency of their occurrence by permitting a smaller total dose of mapharsen without loss of therapeutic effectiveness.

Coutts [145] has treated 13 patients with early syphilis by the use of artificial fever together with a single intravenous injection of arsenoxide and one intramuscular injection of bismuth. All responded favorably to this treatment except 1, a woman, two and a half months pregnant, who had an infectious relapse three months after the one day treatment. Two serious although not fatal reactions are recorded: One patient had hepatitis, and another had anuria with azotemia.

An attempt has been made by Simpson and his co-workers [146] to determine on an experimental basis the value and limitations of a quantitative serologic test for syphilis in relation to clinical response in patients with early syphilis who were subjected to artificial fever therapy alone. It was the original plan of this experiment to treat 25 patients with clinically obvious primary and secondary syphilis with approximately fifty hours of fever with a temperature between 105 and 106 F. Fever was administered in sessions of five hours' duration at weekly intervals for ten weeks. After the first 8 patients were treated by this method, it became obvious that fever therapy alone would not cure early syphilis. It was therefore deemed advisable to abandon this type of treatment because of clinical relapses. However, the following observations were made: The primary or secondary lesions tended to heal after the first few fever treatments, but as this type of treatment progressed, the serologic reactions of the blood for syphilis became more strongly positive. In every instance the progressive rise in titer preceded a clinical relapse.

The same group of workers [147] have studied the serologic response to treatment with combined fever and chemotherapy. Twenty-seven patients with primary or secondary syphilis were treated with combined fever and chemotherapy. The fever was given either in twelve sessions of three hours or in ten sessions of five hours, with temperature levels of 105 to 106 F. The fever was administered once or twice a week. During the course of each fever treatment, patients were given either 0.3 Gm. of neoarsphenamine, or 40 mg. of mapharsen along with 0.2 Gm. of metallic bismuth. A few patients in the group received bismarsen. After the termination of fever treatment, chemotherapy was continued for an additional twenty weeks. All patients in the series were followed for at least four years, the longest period of observation being eight years.

The 27 patients were divided into three groups. The first group comprised 5 male patients with primary syphilis treated twice weekly. In this group all patients

145. Coutts, W. E.: Consideraciones sobre algunos aspectos de venereología contemporánea, Bol. Ofic. san. panam. **21**:1175 (Dec.) 1942.

146. Simpson, W. M.; Rose, D. L., and Kendell, H. W.: Quantitative Serologic Studies in Early Syphilis: I. Treatment with Artificial Fever Alone, Ven. Dis. Inform. **23**:403 (Nov.) 1942.

147. Kendell, H. W.; Rose, D. L., and Simpson, W. M.: Quantitative Serologic Studies in Early Syphilis: II. Treatment with Artificial Fever Combined with Chemotherapy, Ven. Dis. Inform. **23**:408 (Nov.) 1942.

had a reversal to negative of the serologic reaction for syphilis within twenty-three to sixty-four days. Those patients with the highest original titers tended to take the longest time to attain negative serologic reactions. In this group no patient had clinical or serologic relapses.

The second group was comprised of 10 patients, 5 males and 5 females, who had secondary syphilis and who received treatment once a week. Three of these patients had received from one to five injections of an arsenical preparation prior to combined fever and chemotherapy. The titers of all of these patients tended to be somewhat higher than those of the first group, and it took fifty to ninety-three days after treatment was begun to attain negative serologic reactions. Again, those patients with the highest titers had more slow reversal. There were no clinical or serologic relapses in the group.

The third group was composed of 12 persons, 10 males and 2 females, all with secondary syphilis, treated with combined fever and chemotherapy twice a week. Seven of these had received from one to twelve intravenous injections of an arsenical prior to starting fever therapy. The time at which serologic negativity was attained varied between twenty-eight and sixty-six days after treatment was begun. As in the other two groups, without exception, low serum titers tended to reverse more quickly than high serum titers.

Taking the three groups as a whole, no correlation could be observed between the height of the initial serologic titer and the clinical status of the patient. Patients having clinically comparable lesions exhibited great variations in the initial titers. When treatment was adequate, the decline in the serologic titer progressed at a constant rate. There was no appreciable difference in the rate of serologic reversal whether patients received treatment weekly or more intensively, twice weekly.

Since the results obtained by these prolonged courses of combined fever and chemotherapy were so encouraging, the Dayton group sought to compress the duration of treatment into a still shorter period. Twenty-three patients [148] with dark field–positive primary syphilis and strongly positive serologic reactions were subjected to a single ten hour session of artificial fever with a temperature of 106 F., combined with 0.25 Gm. of bismuth subsalicylate in oil, and mapharsen in a total dose varying between 120 and 240 mg. Two patients were given 240 mg. by the continuous intravenous drip method. This procedure was abandoned in favor of the administration of the drug by the syringe method. In the latter case, the drug was given in 60 mg. doses at intervals of three hours; from two to four such doses were administered.

The only complication noted to this combined therapy was the development of transient jaundice. Serologic reactions of the blood for syphilis reversed to negative in twenty-one to one hundred and seventy-six days. There was no correlation between the amount of drug given and the rapidity with which the reactions become negative. The progressive decline of titer to negativity was essentially the same as that noted in persons receiving a larger total amount of both artificial fever and chemotherapy over a longer period. Patients in this group have been followed for six months, during which there have been no serologic relapses.

The cautious statements made by the Dayton workers in these papers regarding the very small series of patients treated by them formed the basis for the outrageously sensational *Reader's Digest* article by de Kruif, "Found—A One Day Cure for Syphilis," commented on unfavorably in the previous review of this

148. Rose, D. L.; Simpson, W. M., and Kendell, H. W.: Quantitative Serologic Studies in Early Syphilis: III. Treatment with a Single Intensive Session of Combined Fever-Chemotherapy, Ven. Dis. Inform. **23**:411 (Nov.) 1942.

series.[1] Physicians, if not the public, will once more be impressed by the conservatism of science and the recklessness of sensational medical journalism.

An editorial writer,[149] commenting on a recent popular article on the so-called "one day cure" for syphilis by combined arsenic-fever therapy, writes:

> The method has very definite hazards. Not everyone can tolerate a fever of 106° F., and patients with certain defects should never be exposed to such a temperature. . . . Too few cases have been treated and too short a time has elapsed to know if there are any late serious effects of the treatment and if the results of the disease are permanent. It may be a step forward in the treatment of syphilis, but much experimental work must be done to be sure that this particular technic is the proper procedure for every case of syphilis. . . .
>
> Physicians can assure their questioning patients that the one-day treatment is in the experimental stage and is not a safe and sure procedure and that it will eventually be made readily available if scientific evidence warrants its acceptance. . . .

Experimental Evaluation of Intensive Methods of Therapy.—In the evaluation of a new drug or a new therapeutic procedure, it is customary to determine toxicity and therapeutic efficacy in the experimental animal prior to clinical trial. However, intensive arsenotherapy of early syphilis has been extensively used without benefit of such experimental data.

A large scale laboratory study by Eagle and Hogan has clarified the situation. These investigators have studied twelve different mapharsen treatment schedules, in which the total duration of treatment varied from ten seconds to six weeks, and in which the frequency of injection varied from standard clinic practice of weekly injections to injections repeated four times daily.

In their first paper, Eagle and Hogan[150] describe the effect on toxicity of mapharsen of varying the method of administration, the frequency of injections and the total duration of treatment. Judged by toxicity in rabbits, the continuous intravenous drip offered no significant advantages over multiple injections. On any schedule of injections, whether weekly, triweekly, daily, several times daily or a continuous intravenous drip, the total amount of mapharsen tolerated can be increased by prolongation of the period of treatment. It is possible, further, to increase the amount of mapharsen which can be given with safety within a given time period by increasing the frequency of injections. Although less drug can be given per injection, the total tolerated dose is thereby significantly increased.

Various methods have recently been suggested for the intensification of antisyphilitic treatment. The decision as to the optimum treatment schedule would be clearly facilitated by a systematic study of the "chemotherapeutic index" (the margin of safety between the amount of drug tolerated and the amount found to be therapeutically effective) as it is affected by varying the frequency of injections and the total duration of treatment. In their second paper Eagle and Hogan[151] present data on the therapeutic activity of mapharsen in experimental rabbit syphilis and on the toxicity-activity ratio (margin of safety) as they are affected by the method of administration. The authors' summary is as follows:

> 1: The total curative dose of mapharsen in syphilitic rabbits (CD_{∞}) was:
>
> (a) 6.3 gm. per kg. for a single injection, and 8.1 mg. per kg. for 6 weekly injections;
>
> (b) 7.7 mg. per kg. for 12 triweekly injections (4 weeks);

149. The One-Day Cure for Syphilis, editorial, New England J. Med. **227**:720 (Nov. 5) 1942.

150. Eagle, H., and Hogan, R. B.: An Experimental Evaluation of Intensive Methods for the Treatment of Early Syphilis: I. Toxicity and Excretion, Ven. Dis. Inform. **24**:33 (Feb.) 1943.

151. Eagle, H., and Hogan, R. B.: An Experimental Evaluation of Intensive Methods for the Treatment of Early Syphilis: II. Therapeutic Efficacy and Margin of Safety, Ven. Dis. Inform. **24**:69 (March) 1943.

(c) 6.3, 3.0, and 6.4 mg. per kg. for daily injections repeated for 1, 4, and 12 days respectively;

(d) 5.9, 6.2, and 3.6 mg. per kg. for multiple injections daily continued for 1, 2, and 4 days respectively; and

(e) 8.9, 6.8, and 11.2 mg. per kg. for an intravenous drip (5 and 6 hours daily) continued for 1, 2, and 4 days respectively.

The dose which cured 50 per cent of the animals in the various schedules was 35 to 75 per cent of the corresponding minimal curative dose.

2. The intravenous drip was significantly less effective than multiple syringe injections administered over the same time period.

3. Comparing the 8 treatment schedules involving syringe injections repeated at varying intervals (2 hours to 1 week), and continued for varying periods (10 seconds to 6 weeks), the curative dose of mapharsen was largely unaffected by the method of administration, varying only between 3.0 and 8.1 mg. per kg. With reservations necessary because of the large experimental error, there was some indication that syringe injections completed in 4 days were more effective than either longer or more intensified schedules. Excluding the two schedules completed within 4 days, the curative dose on the remaining 6 schedules varied only between 5.9 and 8.1 mg. per kg.

4. On any schedule of injections, whether weekly, triweekly, daily, multiple daily, or intravenous drip, any desired margin of safety between the toxic and therapeutic dose of mapharsen could be obtained by appropriate prolongation of the treatment period. The intensification of treatment by arbitrarily decreasing the number of injections, and giving more mapharsen per dose, necessarily resulted in a closer approach to the toxic level, and a narrowed margin of safety.

5. The short-term intravenous drip (1, 2, or 4 days) usually gave an even lower margin of safety (2.1, 4.7, and 4.0 respectively) than did multiple daily syringe injections over the same time period (2.1, 4.3 and 10.6 respectively). This is due to the fact that the intravenous drip was only slightly less toxic, and was usually less effective than schedules involving multiple syringe injections. The margins of safety cited are only a fraction as great as those which could be obtained by prolonged daily, triweekly, or weekly injections.

6. By properly adjusting the total number of injections, the duration of treatment on weekly injections can be cut 50 to 65 per cent *without reducing the margin of safety* by injecting mapharsen triweekly instead of weekly, and can be reduced to an even greater extent by giving injections daily or several times daily. The intravenous drip does not permit a maximal safe condensation of treatment. It is less effective in this respect than daily injections, and only slightly more effective than a triweekly schedule. This is due primarily to its low therapeutic efficacy.

7. An appreciable condensation of treatment beyond that permitted by triweekly, daily, or multiple daily injections can be accomplished only at the cost of safety, by an arbitrary decrease in the total number of injections. Necessarily, more mapharsen must then be given at each injection, with a closer approach to the toxic level, and a proportionate decrease in the margin of safety.

The clinical implications of their experimental study are also discussed by Eagle and Hogan.[152] It is pointed out that in the various intensive treatment schedules which have been used for the treatment of early syphilis in man, the "curative" dose of mapharsen is largely independent of the frequency of injections or the duration of therapy. The curative dose has been 20 to 30 mg. per kilogram, or approximately 1,500 mg. for a man weighing 60 Kg. The margin of safety provided by any intensive therapeutic procedure is therefore primarily a function of its toxicity. The administration of 1,200 mg. of mapharsen by intravenous drip in five days, with a safety factor of 3.0, has resulted in a mortality of 1:200; weekly injection, with a safety factor of 10, has a mortality of less than 1:3,000, and treatment schedules with intermediary factors of safety have resulted in a correspondingly intermediate incidence of deaths.

152. Eagle, H., and Hogan, R. B.: An Experimental Evaluation of Intensive Methods for the Treatment of Early Syphilis: III. Clinical Implications, Ven. Dis. Inform. **24**:159 (June) 1943.

To keep the mortality rate from antisyphilitic treatment less than 1:1,000 it is estimated that a margin of safety of 6 to 8 is required. Any treatment schedule completed in twenty days or less will result in a mortality rate in excess of this. The desired margin of safety is provided, however, by giving the total curative dose in thrice weekly injections for seven to twelve weeks, daily injections for approximately six weeks, or multiple daily injections or an intravenous drip for an estimated period of four to six weeks. Treatment thrice weekly provides almost the maximum condensation of treatment consistent with safety and convenience. It has the advantage of permitting the therapy to be carried out on an ambulant basis. This method is now under study in eighty cooperating clinics.

Kolmer and Rule [153] have determined the toxicity of mapharsen and of neoarsphenamine administered by the intravenous drip method to normal rabbits as compared with the toxicity of these drugs when given by multiple injection. The maximum tolerated dose of mapharsen for rabbits with the continuous intravenous drip method (daily for five days) was about 0.06 Gm. per kilogram of weight; with the syringe method, the single maximum tolerated dose was about 0.015 Gm. per kilogram. The maximum tolerated dose of neoarsphenamine given by five day intravenous drip was about 0.3 Gm. per kilogram, and with the syringe method of administration the single maximum tolerated dose was about 0.225 Gm. per kilogram. The tolerance of rabbits for both compounds appeared better with the continuous intravenous drip method than with the administration of single doses by syringe injection, this being particularly notable in the case of mapharsen.

The arsenic content of the blood of patients with early syphilis treated intensively with multiple injections of mapharsen has been determined by Siegel and his co-workers.[154] Characteristic and essentially similar curves were recorded for 15 patients who received mapharsen alone and 16 patients who received fever therapy with typhoid vaccine in addition to mapharsen. The mean morning values of blood arsenic of patients receiving mapharsen alone showed a progressive rise to 16 micrograms of arsenic per hundred cubic centimeters of whole blood in the course of the first five days of therapy. The mean morning values of blood arsenic of patients who received combined mapharsen and fever therapy showed a prompt rise to about 10 micrograms per hundred cubic centimeters after one day of treatment, remaining essentially unchanged during the next three days and climbed during the next three days to 17 micrograms.

Comparison of these results from the multiple syringe method with the results of observations with the continuous intravenous drip method reveals a close parallelism in morning low point concentrations of blood arsenic obtained with the two methods of administration.

Intensive Arsenotherapy via the Bone Marrow.—Following the demonstration of the feasibility of introducing fluids into the body by way of the bone marrow when veins are inaccessible, as in infants and obese adults, Wile and Schamberg [155] have investigated the possibility of intensive arsenotherapy by this route. Seven rabbits were given massive arsenotherapy by bone marrow infusion drip, 4 mg. of mapharsen per kilogram of body weight each day for five successive days. To

153. Kolmer, J. A., and Rule, A. M.: Mapharsen and Neoarsphenamine Administered by Continuous Intravenous Drip Method: Toxicity for Rabbits, Arch. Dermat. & Syph. **47**:665 (May) 1943.

154. Siegel, J.; Goldstein, D. H., and Goldwater, L. J.: Intensive Treatment of Syphilis with Multiple Injections of Mapharsen: Concentration of Arsenic in the Blood, Arch. Dermat. & Syph. **46**:783 (Dec.) 1942.

155. Wile, U. J., and Schamberg, I. L.: Pulmonary Fat Embolism Following Infusions via the Bone Marrow, J. Invest. Dermat. **5**:173 (Aug.) 1942.

2 control rabbits intravenous massive arsenotherapy was administered. Pulmonary fat emboli, presumable from displacement of fat from the bone marrow, were demonstrated in 5 of the 7 rabbits treated via the bone marrow, whereas no fat emboli were seen in the 2 animals treated by vein. Except for fat embolism, the visceral histologic damage seen in rabbits treated by bone marrow infusion was essentially the same as that noted in rabbits treated by vein. The toxicity of mapharsen did not appear to be altered when administered by the former route. The finding of pulmonary fat emboli in animals treated by bone marrow infusion leads the authors to conclude that the procedure "cannot at present be considered free from hazard in human beings."

Intensive Arsenotherapy in Pregnancy.—Rattner [156] has treated 27 pregnant syphilitic women by five day massive dose arsenotherapy, usually with the concurrent administration of bismuth. The treatment was well tolerated by both mother and fetus regardless of the stage of the pregnancy or the duration of the syphilitic infection. In no case was there a severe reaction or interference with the pregnancy. Of the 27 patients, 1 was lost from observation, 25 gave birth to full term, nonsyphilitic infants, and 1 syphilitic infant was born to a mother who may have acquired a second infection following therapy for the first. In addition to this group, 5 other patients who had been treated intensively subsequently became pregnant and delivered normal children although further antisyphilitic therapy was withheld.

Intensive Arsenotherapy in Congenital Syphilis.—Demonstration of the fact that acquired syphilis in adults can be cured in five days by intensive arsenotherapy has led to the application of this form of therapy to the treatment of congenital and acquired syphilis in infants and children.

Levin and his co-workers [157] have treated 32 infants and children with congenital syphilis and 4 children with early acquired syphilis with massive doses of mapharsen given intravenously over periods of five days. The results of therapy in the group of patients with congenital syphilis were notably inferior to those obtained by similar treatment of early acquired syphilis in adults, and the authors believe that "the spirochetosis of congenital syphilis produces widespread changes more resistant to treatment than acquired syphilis." Of 32 patients with congenital syphilis (12 under 3½ months of age), the serologic reactions of only 12 became negative. In contrast to this, the reactions of all 4 children with early acquired syphilis promptly became negative. Quantitative serologic studies were made in all cases, and a rising titer six months after treatment was considered an indication for a second course of therapy.

The authors properly stress the importance of adequate pediatric care. All of their patients had been examined and had demonstrated their ability to take food and maintain fluid balance before being subjected to the rigorous five day treatment. There were no serious toxic reactions or deaths.

LATE SYPHILIS

Latent Syphilis.—In studying latent syphilis among patients in general hospitals, Gelperin [158] has sought to obtain information by the questionnaire method as to:

156. Rattner, H.: Treatment of Syphilis in Pregnancy by the Five-Day Massive Dose Method, Proc. Inst. Med. Chicago **14**:420 (May 15) 1943.

157. Levin, I. M.; Hoffman, S. J.; Koransky, D. S.; Richter, I. B., and Gumbiner, B.: Congenital and Acquired Syphilis in Infants and Children: Treatment with Massive Doses of Arsenic Intravenously, J. A. M. A. **120**:1373 (Dec. 26) 1942.

158. Gelperin, A.: The Problem of Latent Syphilis in the General Hospital, Am. J. Syph., Gonor. & Ven. Dis. **27**:290 (May) 1943.

(1) the extent of the problem; (2) facilities for follow-up of patients with latent syphilis; (3) whether routine serologic tests are performed, and (4) the percentage of admissions which were free.

Information was obtained from 56 hospitals. Of these, 49 had follow-up services to insure posthospital treatment for patients with early syphilis; next frequent was follow-up for patients with active late manifestations of the disease, and least frequent, similar service for those with latent syphilis. Since it is the last group in whom disastrous late complications develop, a hospital that cares for the indigent sick must begin its attack with the diagnosis of latent syphilis as frequently as possible. The provision of opportunity for antisyphilitic treatment subsequent to the patients' discharge from the hospital is a responsibility shared by the hospital and the local health authority.

Syphilis of the Eye.—A thorough review of the ocular lesions in congenital and in acquired syphilis has been published by Woods.[159] This splendid article, a summary of the entire subject of ocular syphilis, does not lend itself to condensation. Involvement of each of the various structures of the eye is discussed in detail. For a readable and well documented review, the original article should be consulted.

Primary Atrophy of the Optic Nerve.—An evaluation of the results of treatment in 250 cases of syphilitic primary atrophy of the optic nerve followed over many years is detailed by Moore and his co-workers.[160] In their study, primary atrophy of the optic nerve was found to occur in at least 8 per cent of all patients with clinical evidence of acquired neurosyphilis. The incubation period of the condition varied widely, although the majority of patients had onset of symptoms during the second decade of the disease. Atrophy of the optic nerve occurred more than twice as frequently in tabes as in other types of neurosyphilis. In uncomplicated dementia paralytica it was found to be rare.

The therapeutic results were subjected to statistical analysis by the life table method. Among untreated patients, blindness occurred in 28 per cent within one year of onset of symptoms and in 50 per cent within two years, and less than 90 per cent were blind in twelve years. Routine antisyphilitic treatment with trivalent arsenicals and bismuth failed to alter significantly the spontaneous course of the untreated disease. Subdural therapy precipitated blindness in almost 10 per cent of patients. The slight difference between the untreated group and the group receiving subdural therapy could have been due to selection. Of patients given malaria therapy, only 9 per cent were blind at one year after onset of symptoms, 14 per cent were blind at two years, and thereafter, for observation periods up to fifteen years, no additional blindness ensued. In general, the prognosis was less favorable in the presence of central or paracentral scotomas. The authors conclude:

1. Syphilitic primary optic atrophy occurs more frequently in association with tabes dorsalis, though it not infrequently may constitute together with pupillary changes, the only clinical evidence of neurosyphilis. It is probable that the fundamental process is the same in all types of neurosyphilis.

2. The course of the untreated disease is extremely variable. The process almost always becomes bilateral soon after onset of symptoms and 90 per cent of untreated patients are blind within twelve years. There is a small group of patients in whom progression is quite slow.

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159. Woods, A. C.: Syphilis of the Eye, Am. J. Syph., Gonor. & Ven. Dis. **27**:133 (March) 1943.

160. Moore, J. E.; Hahn, R. D.; Woods, A. C., and Sloan, L.: The Treatment of Syphilitic Primary Optic Atrophy, Am. J. Syph., Gonor. & Ven. Dis. **26**:407 (July) 1942.

3. Our data suggest that the development of syphilitic primary optic atrophy can be prevented by the adequate routine treatment of early syphilis.

4. Routine therapy with the trivalent arsenicals and bismuth is not of any value in the treatment of syphilitic primary optic atrophy.

5. Subdural treatment by the Swift-Ellis technique should be abandoned. Its dubious value in an occasional patient is outweighed by a risk of sudden extinguishment of vision in about 10 per cent of those treated.

6. Fever therapy (in our hands malaria, since we have had no experience with the use of mechanically induced fever in this condition) is the only efficacious method of treatment. If visual failure progresses in spite of fever therapy, no other form of therapy is likely to be of value. It must be emphasized that these conclusions are subject to specific limitations imposed by the material upon which this study is based. Since malaria therapy was, by and large, not given to patients with the most rapidly progressive type of disease, no statement is permissible as to its efficacy in this group. It is certain that many of our untreated and routinely treated patients would not have been benefited by any treatment; indeed in many there was literally no time for treatment. The fact remains that where there is time for treatment, malaria is of definite practical value. Since early diagnosis is often possible only by routine determination of the visual fields, fundi, and visual acuity, this procedure is recommended as a routine supplement to the clinical and laboratory examinations in all patients with neurosyphilis. Only by early diagnosis and the immediate induction of malaria is there any hope of arresting the most fulminating cases.

Optochiasmatic Arachnoiditis.—When defects of the visual field occur in a patient with syphilis, they most often indicate parenchymatous disease of the optic nerve which ultimately terminates in atrophy. The possibility of adhesions about the nerves and chiasm nevertheless exists. Syphilis is an etiologic factor in optochiasmatic arachnoiditis, but there are other causes. Ryan [161] reports 3 cases of this condition in which syphilis was excluded as the cause. Tumor of the pituitary gland, hereditary atrophy of the optic nerve (Leber's disease) and glioma of the optic chiasm most frequently enter into the differential diagnosis.

Osseous Lesions.—The diagnosis of osseous lesions associated with acquired syphilis from the viewpoint of the radiologist is discussed by Truog.[162] Nine cases are detailed and the roentgenograms reproduced. In his experience, the osseous lesions of acquired syphilis may simulate many other conditions involving bone. However, the simulation is not complete, since certain characteristic changes of these other conditions are not present. Unfortunately, no information is presented as to the duration of the syphilitic infection in any of the cases. The age of certain of the patients and the destructive nature of the osseous lesions suggest that some of the infections may have been recently acquired. With the author's suggestion that "All syphilitic bone lesions should be referred to as syphilitic osteomyelitis," there should be considerable disagreement. Periostitis and osteoperiostitis not only occur but are indeed the more frequent manifestations of osseous syphilis.

Syphilis of the Larynx.—Wood [163] notes that in the larynx syphilitic lesions do not follow the classic time relationships of the secondary and tertiary periods. Laryngeal involvement may occur with the development of the chancre, and tertiary lesions may accompany or closely follow the secondary stage of the disease.

Early laryngitis is a diffuse serous erythema, with intense swelling and formation of papular thickening of the epithelium. Superficial ulcerations, comparable to mucous patches, frequently occur. Tertiary lesions are diffuse or circumscribed gummatous infiltrations, which may break down to form deeply punched-out

161. Ryan, E. R.: Optochiasmic Arachnoiditis: Report of Three Cases, Arch. Ophth. **29**:818 (May) 1943.

162. Truog, C. P.: Bone Lesions in Acquired Syphilis, Radiology **40**:1 (Jan.) 1943.

163. Wood, E. LeR.: Syphilis of the Larynx, J. M. Soc. New Jersey **40**:15 (Jan.) 1943.

ulcerations. Perichondritis may follow, with necrosis and exfoliation of cartilage. With healing, there may be stenosis and deformity of the larynx. Other laryngeal lesions include paralysis of the vagus nerve in syphilis of the central nervous system and involvement of the recurrent laryngeal nerve from pressure due to aneurysm of the aorta.

Syphilis of the Liver.—In an extensive review dealing with cirrhosis of the liver, Ratnoff and Patek [164] found that of their 386 patients with cirrhosis, 62 (16 per cent) had evidence of syphilis. The high incidence of syphilis among patients with cirrhosis is not readily explained. No correlation between syphilis and alcoholism is present, since syphilis is found as a precursor of cirrhosis in countries where alcoholism is unimportant as a predisposing factor (e. g., Syria and India). Dietary factors may be of importance, but the precise relationship to syphilitic infection is not clear.

Thirty-four of the patients in the series had been treated with arsphenamine or one of its derivatives. Two of these were jaundiced during the period of therapy.

In a review of nonobstructive jaundice, Ottenburg and Spiegel [165] say:

> Disease of the hepatic parenchyma is due either to infections, directly or indirectly, or to chemical agents. The clincial features help little in determining the etiology of a given case. Neither do the new tests of hepatic function. For example, the manifestations of (1) simple (or catarrhal) jaundice, of (2) jaundice following the use of cinchophen or arsphenamine and of (3) the jaundice which occasionally appears in early secondary syphilis, are similar. Most forms of acute hepatic degeneration may progress to a fatal issue with the clinical and histologic characteristics of acute yellow atrophy.

Among the infectious diseases known to cause nonobstructive jaundice is syphilis. In about one half of the fatal cases of congenital syphilis, involvement of the liver occurs, the most characteristic anatomic picture being a diffuse interstitial hepatitis in which huge number of spirochetes are found.

The occurrence of jaundice in secondary syphilis has been recognized for many years. The incidence of jaundice associated with early syphilis is estimated to be between 0.37 and 1.4 per cent. Acute yellow atrophy, according to Ottenberg and Spiegel (though few syphilologists would agree), develops in about 10 per cent of the cases. In one reported series of such cases jaundice appeared from two to four months after the chancre. If the jaundice is untreated its duration may be three weeks to three months. It generally occurs with the secondary lesions but may be present with recurrent cutaneous lesions. Clinically, jaundice associated with secondary syphilis cannot be distinguished from simple jaundice, and the differentiation rests on the presence of chancre or secondary lesions. The jaundice clears promptly after the administration of one of the arsphenamines.

The pathogenesis is disputed, but on the basis of the fairly frequent development of acute yellow atrophy the view of Herxheimer that there is a parenchymatous degeneration seems most acceptable. Spirochetes could not be found in the livers of patients who died.

The authors list all of the chemicals which have been reported to be hepatotoxic agents. These are divided into three groups: first, those causing direct injury to the hepatic parenchyma; second, those causing primary hemolysis with secondary

164. Ratnoff, O. D., and Patek, A. J., Jr.: The Natural History of Laennec's Cirrhosis of the Liver, Medicine **21**:207 (Sept.) 1942.

165. Ottenberg, R., and Spiegel, R.: The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents: Causative Agents, Pathogenesis, Interrelationships, Clinical Characteristics, Medicine **22**:27 (Feb.) 1943.

injury to hepatic cells, and third, those which result in idiosyncrasy, hypersusceptibility and allergic sensitivity in human beings. The arsphenamines fall into the third group.

Distinction is drawn between the early type of postarsphenamine jaundice, which appears within the first week or two after an infection, and the delayed type, which may occur as late as three to ten months after the termination of treatment. The early type is usually associated with a definite time period after the patient receives a given dose of an arsenical, and in most cases there are initial toxic symptoms immediately after the injection, such as fever, chills, gastrointestinal disturbances and toxic erythema. Erythema of the ninth day belongs to this early type. The delayed type of jaundice is more frequent, occurring in about two thirds of all of the cases. The clinical picture may vary from that of simple jaundice to that of acute yellow atrophy.

There has now been demonstrated that there are two types of jaundice following the use of arsenical drugs which can be distinguished on the basis of laboratory tests. With the more common form there are laboratory findings of hepatocellular damage. The less frequent form is characterized by changes suggestive of biliary obstruction, such as elevated values for total blood cholesterol and cholesterol ester, a high concentration of blood phosphatase, and a negative reaction in the cephalin flocculation test. In cases of this type biopsy of the liver shows thrombi in the biliary canaliculi with cholangiolitis similar to that described by Naunyn. This obstructive type is particularly seen in early jaundice or erythema of the ninth day. The point of view that jaundice is dependent on the arsphenamines is based on a number of well known facts, as stated by Ottenberg and Spiegel:

(1) Definite anatomic syphilis of the liver is rarely associated with jaundice.

(2) Arsphenamine jaundice is not accompanied by serologic evidence of recurrence.

(3) Experimentally, arsphenamine does damage the liver functions and large doses can produce jaundice in dogs.

(4) The increased incidence of jaundice is definitely paratherapeutic. . . .

(5) Paratherapeutic jaundice is also observed as a complication in nonsyphilitic cases. . . .

(6) There is occasionally concomitant occurrence of other symptoms of arsphenamine poisoning such as the characteristic dermatitis or the aplastic anemia.

(7) Liver damage has been demonstrated in the latent period of delayed arsphenamine jaundice. . . . A similar variable latent period has been demonstrated with other hepatotoxins, for example, chloroform.

The differential diagnosis between simple jaundice and arsphenamine jaundice is often difficult. An asymptomatic onset, or diarrhea and dermatitis are more common in arsphenamine jaundice, while abdominal pain and tenderness are more frequent in simple jaundice. The authors believe that arsphenamine is of prime importance in most cases of delayed arsphenamine jaundice. However, the occurrence of arsphenamine jaundice with the epidemics of simple jaundice indicates that in some patients the two factors may be synergistic. It must be granted that occasionally simple jaundice may develop in a patient who is receiving antisyphilitic therapy.

Jaundice from bismuth and mercury is briefly discussed. It is believed that these two drugs are hepatotoxic agents but much less frequently than the arsphenamines.

Seeking to determine the effect of syphilitic infection and of antisyphilitic therapy on hepatic function, Vallejo and his co-workers [166] have studied a series

166. Vallejo, V. L.; de la Cuesta, L., and Rodriguez, E.: La prueba de althausen in sifilografia, Rev. argent. de dermatosif. **26**:361, 1942.

of 17 patients with the test of Althausen, one which is concerned with the glycogenic capacity of the liver after the administration of insulin and dextrose. Judging by the results of this test, antisyphilitic therapy is well tolerated by the liver. Occasionally, diminishing hepatic function can be demonstrated, and if this is progressive, as demonstrated by the Althausen test, the authors believe that antisyphilitic treatment should be suspended. Most physicians who treat syphilis no doubt will consider routine tests of hepatic function impracticable in clinic or office practice, however desirable they may be for the early detection of damage to the liver.

CARDIOVASCULAR SYPHILIS

Diagnosis of Aortitis.—Kampmeier, Glass and Fleming [167] believe that for practical purposes the clinical diagnosis of uncomplicated aortitis is impossible. This conclusion was reached after critical analysis of 33 cases of this condition found at postmortem examination, in which clinical and pathologic observations were correlated. Sixteen of the patients had no symptoms referable to the cardiovascular system. The others were found to have pathologic evidence of disease which offered a better explanation for the symptoms and signs than did uncomplicated aortitis. Furthermore, cardiovascular symptoms and signs appeared as commonly in a group of 30 syphilitic persons who presented no evidence of aortitis at necropsy as in those patients who did show such pathologic changes. The authors concede that for an occasional patient with stenosis of the coronary ostiums a diagnosis of uncomplicated syphilitic aortitis may be made with reasonable certainty, but there were no instances of this in their material.

Histologic Changes.—It has long been known that adequate antisyphilitic treatment will bring about clinical and symptomatic improvement in syphilitic aortitis. Restoration of normal structure is not to be expected, since the tissues in the wall of the aorta, once destroyed, cannot be replaced. However, as Howe [168] points out, arrest of the disease by adequate therapy may be correlated with improvement in the histopathologic appearance of the aorta. In a detailed study of 17 treated patients with cases of aortitis, the amount of cellular infiltration into the aortic wall was found inversely proportional to the amount of arsenical therapy received. No correlation was demonstrated between the histopathologic appearance of the aorta and the duration of the syphilitic infection; nor was there any clearcut relationship with intensity or duration of treatment with bismuth or mercury compounds. There was no apparent correlation with the amount of arteriosclerosis or fibrosis.

Cardiovascular Syphilis and the Industrial Employee.—Discussing the importance of cardiovascular syphilis to the industrial physician, Kotte [169] points out that pathologic changes in the ascending aorta are common in patients with clinically latent syphilis and that the early detection of uncomplicated aortitis is exceedingly difficult. In his opinion, every patient with untreated latent syphilis should be regarded as having aortic involvement. Heavy work aggravates the disease in such a person and may be a predisposing factor in the development of aortic dilatation, aneurysm or valvular insufficiency.

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167. Kampmeier, R. H.; Glass, R. M., and Fleming, F. E.: Uncomplicated Syphilitic Aortitis—Can It Be Diagnosed? Ven. Dis. Inform. **23**:254 (July) 1942.

168. Howe, E. G.: The Microscopic Pathologic Appearance of the Aorta in Treated and Untreated Cases of Syphilitic Aortitis, Am. J. Syph., Gonor. & Ven. Dis. **27**:50 (Jan.) 1943.

169. Kotte, J. H.: Cardiovascular Syphilis in the Active Period of Life, Indust. Med. **11**:323 (July) 1942.

Gumma of the Heart.—Spain and Johannsen [170] report that in the department of pathology at Bellevue Hospital there have been seen 3 examples of gumma of the heart. In 1 of the cases there was also found extensive gummatous pulmonary arteritis. Attention is called to the fact that only 17 cases of the latter disease have been reported in the literature.

Case reports and autopsy observations are presented. In all cases, electrocardiograms revealed conduction defects. In 1 case the gumma impinged on both the tricuspid and the pulmonary valve leaflets, resulting in a functional impairment of the valves. In another, the lesion invaded the posterior mitral leaflet and produced stenosis and insufficiency.

Gumma of the heart muscle was about three times as common as diffuse syphilitic myocarditis in the autopsy series of O'Daly.[171] Gummas of the heart may become encapsulated or calcified, or they may undergo central necrosis with weakening of the wall of the heart to produce aneurysmal dilatation. Syphilitic aneurysms of the heart may or may not be associated with aortitis.

Syphilitic Coronary Arteritis.—Syphilitic aortitis resulting in narrowing of the mouths of the coronary arteries is occasionally encountered. Rarely does the process extend more than a few millimeters into the coronary arteries. Marked syphilitic involvement of the coronary arteries throughout a larger portion of the vessels with involvement of the media is rare. Strassmann and Goldstein [172] reported such a case.

A white woman aged 35 became suddenly ill with severe pain in the hypogastrium and died while on the way to the hospital. The principal change seen at autopsy was syphilitic aortitis with narrowing of the mouths of both coronary arteries. The orifice of the left artery was narrowed to a pinpoint; that of the right to a diameter of 1 mm. There was marked concentric thickening of the branches of the coronary arteries throughout their course. The changes usually seen in arteriosclerosis were not present. Striking changes were found in the anterior descending branch of the left coronary artery. A section through the artery about 2 cm. from the mouth showed slight periadventitial and intense adventitial infiltration with lymphocytes and plasma cells. There was also obliterating endarteritis of the vasa vasorum of the adventitia. The most pronounced lesion was found in the media of the left coronary artery, which was completely encircled by a dense infiltrate of lymphocytes and plasma cells. A section stained for elastic tissue demonstrated this cellular infiltrate to extend from the adventitia in some places as far as the intima. In addition, there were destruction of elastic fibers, necrosis and scar tissue formation in other areas of the media. The intima showed an area of marked fibroblastic proliferation with narrowing of the lumen of the vessel.

Burch and Winsor [173] have reviewed the protocols of 6,225 consecutive postmortem examinations at the Charity Hospital at New Orleans to ascertain the incidence of myocardial infarction secondary to syphilitic coronary stenosis. Three instances of this condition were found, and 9 additional cases were added from a review of the literature. A history of severe anginal pain in a middle-aged Negro with a positive serologic reaction for syphilis and no evidence of arteriosclerosis or

170. Spain, D. M., and Johannsen, M. W.: Three Cases of Localized Gummatous Myocarditis, Am. Heart J. **24**:689 (Nov.) 1942.

171. O'Daly, J. A.: Miocarditis gomosa y aneurismas del corazon, Rev. san. y asist. Soc. **8**:77 (Feb.) 1943.

172. Strassmann, G., and Goldstein, P.: Syphilis of the Aorta and Coronary Arteries, Arch. Path. **34**:745 (Oct.) 1942.

173. Burch, G. E., and Winsor, T.: Syphilitic Coronary Stenosis with Myocardial Infarction, Am. Heart J. **24**:740 (Dec.) 1942.

hypertension suggests the possibility of syphilitic coronary stenosis. Approximately one fifth of all patients with syphilitic aortitis have involvement of the coronary ostiums. The condition is frequently associated with aortic regurgitation. The size of the heart depends on the presence of concomitant aortic regurgitation or hypertension. The mean age of patients with coronary involvement was 45 years. Both coronary ostiums were involved in the majority of cases. When myocardial infarction occurs, sudden death is the rule. In all 3 cases reported by the authors, death occurred within a few hours after the coronary occlusion became manifest. Pathologically, the appearance of the myocardium is indistinguishable from that following coronary occlusion secondary to arteriosclerosis. The latter condition not infrequently is superimposed on syphilitic coronary arteritis.

A series of 103 syphilitic patients subject to paroxysmal pain in the chest has been studied by Jones and Bedford,[174] with special regard to the clinical characteristics of the pain and its pathogenesis. There were 80 men and 23 women, a sex ratio of 3.5 to 1. The main clinical findings were aortic regurgitation in 67 cases; dilatation of the aorta in 59; cardiac enlargement, often slight, in 83, and essential hypertension in 26. Electrocardiograms were recorded as abnormal in 57 of the 94 cases in which they were made. Seventy-six patients were subject to angina of effort; 64, to pain apart from effort. Nocturnal attacks were common and usually independent of paroxysmal dyspnea. Attacks tended to be prolonged but were relieved by nitrites. Postmortem observations in 12 cases are given. The common lesions of syphilitic angina were aortitis and aortic regurgitation, usually combined with stenosis of the coronary ostia. There was no evidence that uncomplicated aortitis might cause anginal pain.

Syphilitic Arteritis.—Seeking to determine the frequency of syphilis of the intermediate-sized arteries, Potenza[175] has studied autopsy material from 43 patients with aortitis or aneurysm. In this selected group, 30 (70 per cent) had lesions of the common carotid, the superior mesenteric or the femoral artery. The carotid was involved most commonly, sometimes apparently by continuity from the aorta, and sometimes discrete from the larger vessel. In the 43 patients there were 24 instances of carotid arteritis, 16 of femoral arteritis and 10 of involvement of the superior mesenteric artery. Histologically, infiltration of round cells and destruction of elastic tissue were demonstrated in the media of the vessels, especially about the vasa vasorum.

Aneurysms of the hepatic artery are among the rarer types of vascular lesions. Malloy and Jason[176] note that 85 cases are now on record. In only 7 of these was syphilis the etiologic agent, whereas arteriosclerosis was the cause in 15. The three most frequently encountered symptoms and signs were abdominal pain, hemorrhage into the gastrointestinal tract or abdominal cavity and icterus. Treatment is unsatisfactory and the prognosis grave. Ligation, the only form of surgical therapy employed to date, is dangerous because it is likely to cause death from hepatic necrosis or insufficiency.

Serologic Tests in Cardiovascular Syphilis.—Since most of the papers dealing with the incidence of the positive serologic reaction for syphilis in cardiovascular syphilis include not only cases in which the more modern technics of examination

174. Jones, E., and Bedford, D. E.: Syphilitic Angina Pectoris, Brit. Heart J. **5**:107 (April) 1943.

175. Potenza, L.: Sifilis de las arterias de calibre mediano, Rev. san. y asist. Soc. **8**:103 (Feb.) 1943.

176. Malloy, H. R., and Jason, R. S.: Aneurysm of the Hepatic Artery, Am. J. Surg. **57**:359 (Aug.) 1942.

were used, but also cases in which studies were made in years past with less sensitive tests, Beckh [177] reports the results of serologic tests for syphilis made on the serums of 100 patients with cardiovascular syphilis which came to autopsy between March 1, 1933 and Jan. 12, 1942. During this time the Wassermann and Kahn technics were used, and they were altered at no time during the period.

Of 51 patients with uncomplicated syphiltic aortitis, 86 per cent had positive serologic reactions for syphilis. Of 49 patients with either aortic insufficiency or aneurysm, 88 per cent had positive reactions, and an additional 4 patients, which brings the total to 96 per cent, gave histories of having had either positive reactions at some time in the past or a history of antisyphilitic treatment.

Angiocardiography.—Taylor and McGovern [178] have studied the hearts and aortas of 100 patients with the use of diodrast as a contrast medium for angiocardiography. Included in this group were patients with cardiovascular syphilis. Enlargement of the left ventricular chamber, muscular hypertrophy, regurgitant lesions and aneurysms of the aorta were readily demonstrated by the technic.

The injection of diodrast was controlled by preliminary determination of the circulation time. Reactions to the injections were observed in most subjects, but none was severe enough to warrant discontinuing the injection. The chief reaction was a sharp transient fall in blood pressure.

SYPHILIS OF THE CENTRAL NERVOUS SYSTEM

A symposium on neurosyphilis presented by the Massachusetts Society for Research in Psychiatry [179] affords a review of this subject in the light of present day knowledge.

By way of introduction to the symposium, Perkins [179a] cites data which indicate that substantial progress has been made in making available adequate treatment for dementia paralytica. Comparing the period 1921 to 1930 inclusive with the decade 1931 to 1940, fewer patients with dementia paralytica were admitted to State hospitals, fewer deaths from this cause occurred and the number of patients discharged as improved has increased.

Solomon [179b] notes that "knowledge of paresis and neurosyphilis is more complete than that of any other diagnostic category in psychiatry." Nevertheless, he indicates a number of unsolved problems of diagnosis and therapy still awaiting definite answer.

The long term results of a study of the cases of 268 patients with syphilis of the central nervous system treated with diathermy are presented by Barton and his co-workers.[179c] Having tried several different methods of employing fever therapy, the authors believe the treatment of choice to be electromagnetic induction in a

177. Beckh, W.: The Serologic Reaction in Cardiovascular Syphilis, Am. Heart J. **25**: 307 (March) 1943.

178. Taylor, H. K., and McGovern, T.: Evaluation of Angiocardiography, J. A. M. A. **121**:1270 (April 17) 1943.

179. (*a*) Perkins, C. T.: Progress in Neurosyphilis from a State-Wide Point of View, Dis. Nerv. System **3**:261 (Sept.) 1942. (*b*) Solomon, H. C.: Present-Day Trends in the Investigation of General Paresis, ibid. **3**:262 (Sept.) 1942. (*c*) Barton, W. E.; Borkovic, E. J.; Zuker, J. M., and Malamud, I.: Results of Artificial Fever Therapy in Syphilis of the Central Nervous System, ibid. **3**:264 (Sept.) 1942. (*d*) Kopp, I.: Evaluation of the Clinical and Serologic Results in the Treatment of General Paresis by Malaria, Mechano-Therapy and Tryparsamide, ibid. **3**:270 (Sept.) 1942. (*e*) Freeman, W.: The Relative Efficacy of Various Methods of Treating General Paresis, ibid. **3**:302 (Sept.) 1942. (*f*) Rose, A. S.: Interpretations of the Spinal Fluid in Neurosyphilis, ibid. **3**:280 (Sept.) 1942. (*g*) Rothschild, D., and Sharp, M. L.: Neuropathologic Features of General Paresis in Relation to Mental Disturbances, ibid. **3**:310 (Sept.) 1942.

humidified cabinet, the patient's temperature being brought to 106 F. and maintained at that level for four hours for each of seven periods spaced not more frequently than every other day. The course is repeated after six months if deemed necessary. Continuous chemotherapy with tryparsamide, bismuth and mapharsen in alternate courses is given on completion of the fever treatment.

Kopp,[179d] on the other hand, believes a combination of fever and tryparsamide to be most effective. His results with malaria therapy are superior to those obtained with artificial fever when both are followed by prolonged chemotherapy.

Freeman [179e] disagrees, and says that malarial therapy combined with chemotherapy was not as effective as diathermy fever in combination with similar chemotherapy. In his experience, active specific therapy reduces the death rate from dementia paralytica regardless of the patients' age. Acute infections, especially of the respiratory tract, are the most frequent cause of death of patients with this disease.

Discussing he results of examination of the spinal fluid in cases of neurosyphilis, Rose [179f] says he has found that in parenchymatous syphilis of the central nervous system the spinal fluid returns to normal more slowly than in other types. Return of the spinal fluid to normal in one year or less is considered to be evidence against the diagnosis of dementia paralytica regardless of the clinical symptoms or treatment. An early return of the total protein content and the cell count to normal levels is a fair indication of a satisfactory outcome.

The relationship between neuropathologic changes and mental disturbances in 17 cases of dementia paralytica is discussed by Rothschild and Sharp.[179g] In 13 of these cases the severity of the clinical disturbances showed a fairly close correlation with the neuropathologic abnormalities. In 4 cases a lack of correlation was observed, and in this group personality factors seemed to play a role. It is suggested that a favorable outcome in dementia paralytica depends not only on effective antisyphilitic therapy but also on the integration of the patient's personality.

Analyzing the cases of neurosyphilis admitted to the Ontario Hospital, London, Ontario, Canada, during the five year period 1936 to 1940, McCausland and Straker [180] found a steady decline in the admission rate of patients with syphilis of the central nervous system. Two facts appear from the analysis: (1) Few patients admitted to a hospital for persons with mental disease previously had received adequate antisyphilitic treatment, and (2) patients who had received treatment prior to hospitalization had the best prognosis. Of the treated group, those receiving both malaria therapy and tryparsamide had the most favorable outcome.

Syphilis of the Cerebral Veins.—Syphilitic lesions of the cerebral arteries and arterioles are not uncommon. Little attention has been given, however, to the changes in the central nervous system resulting from syphilis of the cerebral veins in the absence of appreciable arterial involvement. Marsh [181] states that the pathologic changes in the cerebral veins are much the same as those occurring in the arteries. Primary involvement of the veins in the absence of arterial changes is difficult to establish because impairment of venous circulation alone is rarely fatal. By the time death ensues there usually is advanced involvement of both arteries and veins. The author's case report concerns a patient with meningovascular neurosyphilis whose death was due to thrombosis of the superior cerebral veins.

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180. McCausland, A., and Straker, M.: An Analysis of Neurosyphilis Over a Five-Year Period, Canad. M. A. J. **47**:240 (Sept.) 1942.

181. Marsh, C.: Thrombosis of the Superior Cerebral Veins as a Consequence of Meningovascular Syphilis, Bull. Los Angeles Neurol. Soc. **8**:18 (March) 1943.

Tabetic Arthropathy.—Steindler, Williams and Guri,[182] who have observed 134 patients with 214 Charcot joints, discuss this lesion in detail. In only 57 patients was there outspoken evidence of tabes dorsalis, and no less than 76 patients had symptoms referable to the joint as the first of which they complained. Manifestations detected by roentgen examination included: osteosclerosis, fragmentation, absorption of bone, free body formation, exostoses and new bone formation, extra-articular ossification, osteoporosis, pathologic fracture, dislocation, disalinement and effusion.

In this series the knee joint was most frequently involved (50.9 per cent). For the treatment of Charcot's knee, the authors recommend a well fitted long leg brace entirely immobilizing the joint, supplied with a tuber seat arrangement to eliminate weight bearing. The operative treatment of choice in early stages is fusion rather than resection.

Charcot joints most often occur in the knee, ankle, hip and shoulder. More rarely they appear in the articulations of the vertebral column. The characteristics of the lesion when the vertebral bones are involved are discussed by Amyot, Vasquez and Genest.[183] This lesion is in itself painless, but it may produce pain of the radicular type by compression of the spinal nerves through the formation of osteophytes or through destruction of the intervertebral disk. All parts of the articulation may be involved in the destructive process. The authors believe that local vasodilatation with congestive stasis is a factor in the genesis of trophic osteoarthropathy.

Orthostatic Hypotension in the Tabetic Form of Dementia Paralytica.—Orthostatic hypotension, previously reported in association with tabes dorsalis, also occurs in the tabetic form of dementia paralytica, as reported by Freeman and Robertson,[184] who note that the condition does not prevent administration of malarial therapy. The diagnostic features of the condition include: (1) decrease in systolic and diastolic blood pressure, with vertigo, diplopia and occasionally syncope when the patient rises to the erect position; (2) generalized or localized diminution of perspiration; (3) failure of the pulse rate to increase normally after exercise or when the erect position is assumed; (4) relative recumbent diuresis, as compared with the output of urine when the patient is erect; (5) accentuation of symptoms during hot weather; (6) loss of libido and potentia, and (7) often a low basal metabolic rate, increased blood urea nitrogen and decreased excretion of phenolsulfonphthalein.

Lissauer's Type of Dementia Paralytica.—Dementia paralytica in which focal symptoms are a predominant feature and there are circumscribed areas of atrophy in one or both cerebral hemispheres has come to be known as Lissauer's type. Various theories have been advanced to explain its pathogenesis. Some have believed the changes within the areas of atrophy were merely regions of increased reactivity to invasion by S. pallida. Others have thought that cerebral endarteritis contributes to the picture. Altered permeability of the cerebral vessels, "toxic" products and changes in the colloidal state of the cerebral tissues have also been advanced to explain this unusual type of syphilitic process. The studies of Galbraith

182. Steindler, A.; Williams, L. A., and Guri, J. P.: Tabetic Arthropathies, Urol. & Cutan. Rev. **46**:633 (Oct.) 1942.

183. Amyot, R.; Vasquez, J., and Genest, A.: Ostéo-arthropathie tabétique de la colonne vertebrale, Union méd. du Canada **72**:305 (March) 1943.

184. Freeman, H. E., and Robertson, J. E.: Orthostatic Hypotension Accompanying the Tabetic Form of Dementia Paralytica, Arch. Dermat. & Syph. **46**:796 (Dec.) 1942.

and Meyer [185] support the view that the process underlying the focal manifestations is essentially inflammatory, a localized intensification of the usual pathologic process of dementia paralytica. Vascular changes are admitted to occur, but these, they think, are secondary to the inflammatory process. Histologic studies show that the areas of inflammation, which later become atrophic, are most often situated in the posterior parts of the cerebral cortex.

Adie's Syndrome.—Adie's syndrome, a symptom complex of absence of tendon reflexes and tonic pupils, is of importance in that it must be differentiated from tabes dorsalis. Dynes [186] describes the clinical aspects of the syndrome. In the series of 8 cases, which he reports, symptoms of nervousness, emotional disturbance, palpitation, sweating and the associated anxiety and fear states frequently were encountered. This confirmed previous observations that instability of the autonomic nervous system is commonly associated with the tonic pupils and areflexia. Blurring of vision, occasional ocular pain or photophobia may accompany the pupillary abnormality. The author stresses the fact that Adie's syndrome is a benign disorder and requires no therapy unless it be psychotherapy, particularly if the patients previously have been told that they suffer from syphilis.

Adie described the pupillotonic phenomena as being unilateral, with the tonic pupil considerably larger than the nontonic pupil. About 80 per cent of the persons affected are females, the majority of them being young. The tonic pupil is usually oval, with either vertical or horizontal orientation. To the usual methods of examining pupils by flashlight the reaction to light, direct and consensual, is completely or almost completely absent. When the person is in the darkness for an hour the pupil dilates, and when he comes into bright light a sluggish contraction may be observed, so that the pupil becomes narrower than before it was in the darkness. The pupil finally contracts to a point where it is smaller than the normal pupil. The Adie pupil is said to dilate readily with mydriatics and to contract with physostigmine.

Adie believes that the factor responsible for the tonic pupil is of sympathetic origin. He agrees that the site of the disturbance of the pupils is the sympathetic part of the nucleus of the third nerve. Adie and many others do not believe that this type of pupil is associated with a syphilitic infection. However, there are those who have not agreed with this impression.

Lowenstein and Friedman [187] have studied true Adie pupils and Adie-like pupils associated with syphilis. They conclude as follows:

1. Pupillotonic reactions may be caused by peripheral lesions of the third nerve both postganglionic and preganglionic and by lesions in the great vegetative centers of the diencephalon and their connections with the mesencephalon.

2. Adie's syndrome is due to heredodegenerative disease localized in the great autonomic centers of the diencephalon and their connections with the mesencephalon. It is characterized by pupillotonic reactions with irritative (not paralytic, like the Horner-Bernard syndrome) sympathetic symptoms and absence of tendon reflexes. It generally has no syphilitic etiologic factor but as a syndrome may be produced by so-called asymptomatic syphilis nervosa.

3. As the nervous manifestations of congenital syphilis (more frequently than of acquired syphilis) are frequently localized in the sympathetic center, there is a possibility that in some cases Adie's syndrome is due to congenital syphilis.

4. The pupillographic picture of Adie's syndrome is generally unequivocal.

185. Galbraith, A. J., and Meyer, A.: Lissauer's Dementia Paralytica, J. Neurol. & Psychiat. **5**:22 (Jan.-April) 1942.

186. Dynes, J. B.: Adie's Syndrome: Its Recognition and Importance, J. A. M. A. **119**: 1495 (Aug. 29) 1942.

187. Lowenstein, O., and Friedman, E. D.: Adie's Syndrome (Pupillotonic Pseudotabes), Arch. Ophth. **28**:1042 (Dec.) 1942.

5. Physostigmine contracts the Adie pupil like the normal pupil; however, it restores the ability of the Adie pupil (in twelve to twenty minutes after its local application) to react to light and to dilate to distant vision.

6. The physostigmine test in cases of questionable diagnosis enables one to differentiate Adie's syndrome from similar syndromes due to acquired syphilitic infection.

7. Neurotonia characterized by a prompt contraction of the pupil to light but a sluggish and retarded dilation (sometimes after a latency period of more than five minutes) and by a convergence reaction which may be unilaterally or bilaterally diminished or absent appears to be an inversion of Adie's syndrome. The relation with Adie's syndrome is shown by the fact that either syndrome may be substituted for the other in the hereditary sequence; therefore, the basic processes must be considered identical.

8. The clinical entities of neurotonia and pupillotonic pseudotabes include many minor and abortive forms which can be detected by pupillography; they are not rare but are rather frequent anomalies and have the value of a focal stigma degenerationis in the nervous system.

Leathart [188] discusses the physical signs of Adie's syndrome and the anatomy of the ocular reflexes concerned. The author believes that the physical signs of the syndrome can be produced by destruction of the ciliary ganglion, and he postulates defective conduction between preganglionic and postganglionic fibers in this structure. Also postulated is a lesion in the sacral and lumbar segments of the spinal cord producing the areflexia in the knee and ankle jerks—a lesion in the intercalated fibers connecting the posterior root fibers with the anterior horn cells, possibly resulting in faulty conduction in the synapses there, analogous to the abnormalities in the ciliary ganglion with the loss of the light reflex.

The Catatonic Pupil.—The so-called catatonic pupil is characterized by inequality in size, inconstancy in reaction and sluggishness or complete abolition of the light reflex. Levine and Schilder [189] have studied this pupillary abnormality and believe it is due to paralysis or inhibition of the parasympathetic nervous system. They point out that when a person exerts pressure, as in squeezing some object, both the normal and the catatonic pupil become dilated and less rapidly reactive to light. By this procedure it may be possible to bring out latent pupillary defects. The Argyll Robertson pupil is not affected by the procedure, nor is the tonic pupil of Adie. The effect of mydriatic drugs can be enhanced by the procedure until the drugs cause complete mydriasis.

Pathways of Pupillary Contraction.—Nathan and Turner [190] present evidence to show that there are two efferent pathways for pupillary contraction: one serving the light reflex and the other the accommodation-convergence synkinesia.

It is usually believed that pupilloconstrictor fibers leave the nucleus of the third nerve and run with the nerve to the inferior oblique muscle, branching off from this nerve to relay in the ciliary ganglion. Distal to the ganglion they form several short ciliary nerves, which pierce the sclera around the optic nerve and form the ciliary plexus, from which fibers to the sphincter muscles of the iris are derived.

If this were the only pathway by which constrictor fibers reach the sphincter, complete interruption of this pathway should cause paralysis of the reaction to light and in accommodation. Cases are described, however, which show that the Argyll-Robertson pupil may be caused by damage to the peripheral efferent path-

188. Leathart, P. W.: The Tonic Pupil Syndrome, Brit. J. Ophth. **26**:60 (Feb.) 1942.

189. Levine, A., and Schilder, P.: The Catatonic Pupil, J. Nerv. & Ment. Dis. **96**:1 (July) 1942.

190. Nathan, P. W., and Turner, J. W. A.: The Efferent Pathway for Pupillary Contraction, Brain **65**:343 (Dec.) 1942.

way to the pupil. Some other pathway must therefore be available. The authors believe this second pathway may run from the third nucleus to the episcleral ciliary ganglion and thence relay to the ciliary body, without passing through the ciliary ganglion.

Syphilitic Papilledema.—Involvement of the optic nerves in syphilitic meningitis about the optic chiasm has been reported several times in the past. In these cases syphilitic arachnoiditis caused primary atrophy of the optic nerves. Hausman [191] reports the occurrence in 2 patients of syphilitic papilledema without increase in intracranial pressure. When atrophy of the optic nerves appeared it was secondary to the papilledema. In 1 of the cases papilledema was associated with a moderate degree of internal hydrocephalus, dilatation of the chiasmal cistern and thickening of the arachnoid. In the other the cause was a gummatous meningitis around the optic chiasm and nerves. In neither case was there any significant increase in the cerebrospinal fluid pressure.

Fever Therapy.—The changes produced in cerebral blood sugar, lactic acid and p_H by elevation of temperature in 12 patients with dementia paralytica being treated by diathermy have been studied by Looney and Borkovic.[192] They report a slight increase in utilization of sugar and a significant increase in p_H. The arteriovenous difference in lactic acid was reversed so that during the febrile period lactic acid was produced. This may explain, in part, the slight increase in the arteriovenous difference in blood sugar. The findings confirm previous reports that there is no increase in brain metabolism during diathermy.

The use of oxygen during the period of artificial fever therapy has been instituted on the basis that the increase in metabolism coincident with the increase in body temperature requires a greater amount of oxygen than can be acquired by normal respiration. Cullen, Weir and Cook [193] find the use of oxygen during fever therapy beneficial. Patients receiving oxygen have less tachycardia and require less sedatives. Restlessness, mental confusion and excitement are less frequent and less marked than in those who do not receive oxygen.

Electric Shock Therapy.—After using nonconvulsive electric (faradic) shock therapy for 5 patients with dementia paralytica, Berkwitz [194] reports that acute delirious reactions responded favorably. Subsequent treatment with malaria and chemotherapy resulted in improvement in the clinical signs and in the abnormalities in the spinal fluid.

Electric shock treatment of patients with psychoses associated with dementia paralytica has been attempted by Heilbrunn and Feldman.[195] Five patients whose psychotic manifestations had failed to improve from fever and chemotherapy were chosen. Alternating electric current was employed, the electrodes being applied at the temples. The initial amount of current usually was 250 to 350 milliamperes for three-tenths second at a tension of 60 to 70 volts. The "dosage" was gradually

191. Hausman, L.: Syphilitic Papilledema Without Increase in Intracranial Pressure: Its Relation to Lesions at the Chiasm, J. Mt. Sinai Hosp. **9**:522 (Nov.-Dec.) 1942.

192. Looney, J. M., and Borkovic, E. J.: The Effect of Diathermy on Brain Metabolism: Changes Produced on the Sugar, Lactic Acid and p_H of the Arterial and Venous Blood of the Brain in Paretic Patients, J. Lab. & Clin. Med. **28**:983 (May) 1943.

193. Cullen, S. C.; Weir, E. F., and Cook, E.: The Rationale of Oxygen Therapy During Fever Therapy, Arch. Phys. Therapy **23**:529 (Sept.) 1942.

194. Berkwitz, N. J.: Non-Convulsive Electric (Faradic) Shock Therapy of Psychoses Associated with Alcoholism, Drug Intoxication and Syphilis, Am. J. Psychiat. **99**:364 (Nov.) 1942.

195. Heilbrunn, G., and Feldman, P.: Electric Shock Treatment in General Paresis, Am. J. Psychiat. **99**:702 (March) 1943.

increased until a convulsant dose was found. The treatment was given two to three times a week. The procedure proved to be a perilous one. Cardiovascular or respiratory failure necessitated discontinuance of the treatment before any clinical improvement was noticeable. The authors attribute the severe complications to a heightened vulnerability of the ganglion cells of patients with syphilitic meningoencephalitis.

Malaria Therapy.—Kopp and Solomon [196] call attention to the fact that in therapeutic malaria transient disturbances in hepatic function may be noted. Performing a variety of tests of hepatic function on 9 male patients under treatment for dementia paralytica with inoculation malaria, these authors found indications of decreased hepatic function in reduction in percentages of total blood cholesterol and cholesterol ester, in lowered excretion of hippuric acid and in strongly positive reactions to cephalin flocculation tests. Less marked were reduction of phospholipid, retention of bromsulphthalein and changes in bilirubin. Impairment of hepatic function was transient, usually clearing within three to six weeks after termination of the malaria.

Of interest in the management of syphilitic patients being treated with therapeutic malaria is the observation that jaundice occasionally occurs after termination of the malaria and after the administration of the first few injections of an arsenical. The authors believe that the administration of arsenicals after the malaria treatment and before function of the liver has returned to normal may overburden the liver and result in jaundice.

Sodium bismuth thioglycollate has been shown to reduce the frequency of malarial paroxysms without eliminating them altogether. Young, McLendon and Smarr [197] have sought to determine (1) at what age the parasites are affected by the drug and (2) whether species of malaria parasites other than Plasmodium vivax can be controlled similarly. In 0.1 to 0.2 Gm. amounts, this compound was found to have an inhibitory effect against P. vivax parasites which are half grown, i. e., those obtained about sixteen to twenty-eight hours after a paroxysm. Parasites older or younger were not affected. Use of the drug at this time converted paroxysms from quotidian to tertian periodicity; and paroxysms converted to tertian in type usually remained so during the remainder of the infection. No significant effect of sodium bismuth thioglycollate could be demonstrated against either Plasmodium malariae or Plasmodium falciparum.

Intraspinal Injection of Thiamine Hydrochloride.—Stone [198] has administered thiamine hydrochloride intraspinally combined with vitamin E and vitamin B complex orally to 63 patients with neurosyphilis, and he recommends this as a valuable adjunct in the treatment of neurosyphilis. In his experience, patients with tabes dorsalis show marked improvement in gait, symptoms involving the bladder, visual disturbances and lightning pains. In patients with dementia paralytica an increased tolerance to fever therapy was noted and fewer hours of fever were needed to produce a remission. There was, however, no definite effect on the psychoses of patients who failed to improve under previously administered fever therapy following additional intraspinal and oral vitamin medication.

196. Kopp, I., and Solomon, H. C.: Liver Function in Therapeutic Malaria, Am. J. M. Sc. **205**:90 (Jan.) 1943.

197. Young, M. D.; McLendon, S. B., and Smarr, R. G.: The Selective Action of Thiobismol on Induced Malaria, J. A. M. A. **112**:492 (June 19) 1943.

198. Stone, S.: Non-Specific Therapy of Neurosyphilis: Results from Intraspinal Administration of Thiamin Chloride Combined with Vitamin B Complex and Vitamin E (Wheat Germ Oil), Urol. & Cutan. Rev. **46**:714 (Nov.) 1942.

Cisternal Puncture.—Over a period of ten years, 6,123 diagnostic cisternal punctures have been performed at the Dallas Syphilis and Venereal Disease Clinic. Alexander, Fox and Schoch [199] report that in this series no fatalities have resulted nor any reaction of serious consequence. Few of the patients, all of whom were ambulatory, had headaches which were severe enough to cause them to complain, and no headaches were so severe as to require rest in bed. The authors believe that in competent hands cisternal puncture is a valuable procedure, which should be more widely used. They do not consider the procedure too dangerous for routine use.

Post-Lumbar-Puncture Headache.—Favorable results from the treatment of post-lumbar-puncture headache with ergotamine tartrate are reported by Guttman.[200] Thirty-five patients on whom lumbar puncture had been performed and spinal anesthesia induced were treated for post-puncture headache with this drug (0.25 to 0.50 mg., given either intravenously or intramuscularly). When given according to the tolerance of the patient, ergotamine tartrate was found to be of value in relieving headache in 80 to 90 per cent of the persons treated.

CONGENITAL SYPHILIS

Dental Changes.—A comprehensive review of the dental changes in congenital syphilis is presented by Sarnat and Shaw.[201] A group of 73 patients with congenital syphilis was studied, and 22 (30 per cent) were found to have characteristic dental changes.

The effects of the disease are different in the growing deciduous and permanent teeth. The deciduous teeth, active in the formation of enamel, show developmental disturbances in that structure; the permanent teeth, active in morphodifferentiation, show disturbances at the dentoenamel junction, with a resulting characteristic dwarfing of the crown. The pathognomonic convergence of the lateral surfaces of the permanent upper central incisors should not be confused with hypoplasia of the enamel, which occurs at a later time and which may be caused by rickets, hypoparathyroidism or fluorosis.

The teeth which are affected and may be of diagnostic value in congenital syphilis are the permanent upper central incisors, lower central and lateral incisors and first molars. Both the incisors and the first molars were found to have a convergence of the lateral surfaces. In addition to decreased occlusal surface of the permanent first molars, the cusps frequently are crowded together, and caries not uncommonly is superimposed. Dental dystrophy occurs early and is permanent.

A comparison of the ground sections of Hutchinson teeth and of normal incisors revealed differences in the size and form of the dentoenamel junctions but no significant structural differences in the enamel and dentin. Roentgenographic examination revealed the characteristic convergence of the sides of incisors and molars, and this abnormality was demonstrable prior to eruption of the teeth.

Saddle Nose Deformity.—A not infrequent facial deformity resulting from syphilitic infection, either congenital or acquired, is the saddle nose. Persons afflicted with this unsightly deformity benefit both physically and mentally from operative correction. Fleming [202] discusses the operative technic for the correction

199. Alexander, L. J.; Fox, E. C., and Schoch, A. G.: Cisternal Puncture: Favorable Report Based on Over Six Thousand Punctures, Arch. Dermat. & Syph. **46**:725 (Nov.) 1942.

200. Guttman, S. A.: Treatment of Post-Lumbar-Puncture Headache with Ergotamine Tartrate, Arch. Neurol. & Psychiat. **49**:556 (April) 1943.

201. Sarnat. B. G., and Shaw, N. G.: Dental Development in Congenital Syphilis, Am. J. Dis. Child. **64**:771 (Nov.) 1942.

202. Fleming, P. N.: The Saddle Nose, Dis. Eye, Ear, Nose & Throat **2**:244 (Aug.) 1942.

of the saddle nose deformity, stressing adequate preoperative preparation, meticulous aseptic technic and the fact that several procedures may be necessary before a satisfactory result is attained. To fill in the bony defect the author recommends implantation of a small piece of ivory, rib cartilage or tibial graft. Of these, ivory offers the best cosmetic result, since it can be readily shaped and may be sterilized before use.

Effect of Bismuth on Growth of Bone.—Administration of bismuth in amounts such as are used in the treatment of patients with syphilis causes abnormalities at the site of provisional ossification of growing long bones. These abnormalities appear to consist chiefly of the persistence of matrix substance at the metaphysial line beyond the time when normally it would be removed. These metaphysial changes occur only when bone is still in the process of growth.

Because these bony abnormalities occur at the area of growth of the long bones and because linear growth of the body is dependent on osseous growth, Russin, Stadler and Jeans [203] have studied the effect of long-continued antisyphilitic therapy on the stature of children. They interpret their data as showing that antisyphilitic treatment has no adverse effect on ultimate bone or body length. Of the 10 children included in the study, the majority grew at average rates. Five exceeded the predicted height by 2 inches (5 cm.) or more, and three had heights 2 or more inches less than predicted. For the entire group the average difference between actual and predicted height was zero.

Cardiovascular Involvement.—In a lengthy and detailed review of the literature pertaining to cardiovascular involvement in congenital syphilis, Hinrichsen [204] concludes:

> Reports in the literature show that congenital syphilis produces definite myocardial lesions of two types, namely, interstitial and nodular myocarditis, in which spirochetes can be demonstrated. No evidence can be found that congenital syphilis produces valvular heart lesions. The role of this disease in the production of aortitis and aneurysm and in the production of congenital malformations of the heart has not been determined definitely. Further study is required. Syphilitic arteritis, particularly cerebral arteritis, may be produced by congenital syphilis. It is possible that congenital syphilis is a factor in the production of arteriosclerosis and of Raynaud's disease. Congenital syphilis is one of the causes of hemorrhagic disease in the newborn infant.

Resemblance to Erythroblastosis.—Having studied 53 infants with erythroblastosis, Henderson [205] discusses the differentiation between this condition and congenital syphilis. The two diseases have several features in common: frequent occurrence of premature birth, erythropoietic response to toxic hemolysis, cirrhosis of the liver and placental abnormalities. It is pointed out that serologic tests for syphilis, the demonstration of S. pallida or the occurrence of osteochondritis may assist in the differentiation. The tendency is for congenital syphilis to become progressively less severe in succeeding pregnancies, whereas in erythroblastosis the trend is in the opposite direction.

Treatment with Acetarsone.—In the past decade, much has been written about the treatment of congenital syphilis with acetarsone. Preliminary reports were favorable, even enthusiastic, but more recently the effectiveness of this oral

203. Russin, L. A.; Stadler, H. E., and Jeans, P. C.: The Bismuth Lines of Long Bones in Relation to Linear Growth, J. Pediat. **21**:211 (Aug.) 1942.

204. Hinrichsen, J.: Cardiovascular Involvement in Congenital Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **27**:319 (May) 1943.

205. Henderson, J. L.: Erythroblastosis or Congenital Syphilis: Observations on Erythroblastosis and Its Differential Diagnosis from Congenital Syphilis, J. Obst. & Gynaec. Brit. Emp. **49**:499 (Oct.) 1942.

spirocheticide has been questioned. Arena [206] reviews the advantages of acetarsone as well as the objections that have been raised to its use. In his own experience, the oral use of acetarsone is both advantageous and effectual. This route of administration should be used for infants under 1 year of age, since mothers will carry out the treatment. Older infants should be given arsenicals parenterally, since the injections can be given without undue difficulty and the results are better.

In monographic form, published as a supplement to *Venereal Disease Information*, Hinrichsen [207] reviews the literature pertaining to the use of acetarsone in the treatment of congenital syphilis. The experimental studies of the drug in animals, its toxic effects in adults, and its therapeutic effect in adult syphilis are considered in detail because of the direct relationship they bear to the problem of treatment of congenital syphilis. Most observers are agreed that the antisyphilitic action of acetarsone is considerably inferior to that of arsphenamine. Some have found its action to be about the same as that of bismuth, while others consider its action inferior to that of bismuth. The only apparent reason for the use of acetarsone in the treatment of congenital syphilis is the fact that it can be given by mouth. This advantage is offset, however, by the fact that the physician can never be sure that the treatment prescribed actually has been given.

The results of experimental studies of acetarsone in animals show marked variations in toxicity as determined by different investigators and also among the animals of any single investigator. The same variable and unpredictable results were obtained in the prophylactic and curative treatment of animals infected experimentally. That acetarsone is a highly toxic drug is apparent from the number and severity of the toxic reactions which have been reported to occur both in adults and in children. Analysis of the therapeutic results with the drug is difficult because of the many extraneous factors.

The author believes that all the evidence on hand supports the contention that acetarsone is far from being the "ideal" drug for the treatment of infantile congenital syphilis and that it is of very limited usefulness in syphilotherapy.

Treatment with Mapharsen.—Astrachan and Cornell [208] find mapharsen an effective drug for the treatment of both early and late congenital syphilis. In their opinion, the dosage of mapharsen should not exceed 0.75 mg. per kilogram of weight.

Of 68 patients with congenital syphilis, 57 were in the late stages of the disease and 11 in the early stages. These patients received a total of 1,507 injections of mapharsen, 495 of these being administered intramuscularly. Few untoward reactions were noted, and the authors believe the drug is even less toxic to children than to adults.

As to the feasibility of intramuscular administration of mapharsen, it is stressed that, while some patients complained of severe and persistent pain at the site of injection, the majority of the injections were followed by slight or moderate pain only, that no areas of necrosis developed and that serious systemic complications did not appear as a result of this method of administration. In selected cases, the intramuscular route may be used, but it should be employed cautiously, with

206. Arena, J. M.: The Treatment of Congenital Syphilis with Acetarsone (Stovarsol): The Result of a Ten-Year Study, South. M. J. **36**:201 (March) 1943.

207. Hinrichsen, J.: Acetarsone in the Tratment of Congenital Syphilis, Ven. Dis. Inform., 1942, supp. 18, p. 1.

208. Astrachan, G. D., and Cornell, V.: Mapharsen in the Treatment of Congenital Syphilis, with Especial Consideration of the Intramuscular Method of Administration, J. A. M. A. **121**:746 (March 6) 1943.

gradually increasing doses, and only in those cases in which all attempts at intravenous therapy have failed.

Congenital Syphilis as a Cause of Infant Mortality.—A comparative mortality study in 859 cases of premature birth at the Charity Hospital of Louisiana for a period of the years 1937 to 1940 inclusive is given by Flax, Levert and Strong.[209] The mortality rate among premature infants in 1937 was 85.3 per cent, and in 1940, 42.2 per cent. There was a gradual yearly decrease in the mortality rate, which could be accounted for primarily on the better care of premature infants.

There were 498 deaths of premature infants in the entire group. The main causes of death were as follows: atelectasis, 24.22 per cent; prematurity, 22.08 per cent; bronchopneumonia, 15.07 per cent; diarrhea, 12.44 per cent; cranial injury, 11.05 per cent; syphilis, 4.61 per cent; and all other causes, 10.44 per cent. In some instances it was impossible to arrive at any diagnosis other than prematurity.

Third Generation Syphilis.—The question of the transmission of syphilis to the children of those who themselves have acquired the disease in utero (third generation syphilis) is still debatable. Beerman, Wammock and Magnuson[210] have analyzed the cases of third generation syphilis published since 1933, noting that in no instance has a really indubitable example been recorded. They discuss in detail a patient whose clinical course and whose parents' and grandparents' infections were studied carefully. The patient, in all probability, had third generation syphilis.

SYPHILIS AND OTHER DISEASES

Syphilis and Cancer.—A study has been made by Levin and his co-workers[211] to determine the relationship between syphilis and cancer by determining the prevalence of reported syphilis among patients with cancer reported to the New York State Health Department. The data appear to confirm the previously reported high prevalence of syphilis among males with cancer of the tongue and among white females with cancer of the cervix.

Evidence for the diagnosis of syphilis consisted of (*a*) physical manifestations of tertiary syphilis in 26 cases; (*b*) at least two positive serologic reactions and a history of infection or treatment in 39 cases; (*c*) a single positive serologic reaction and a history of infection or treatment in 12 cases; (*d*) at least two positive serologic reactions in 42 cases; and (*e*) a single positive serologic reaction alone in 58 cases.

Among males with cancer of the tongue, the prevalence of syphilis was approximately five times as great as among males with cancer of all other sites. Among females with cancer of the cervix, the corresponding ratio was 3.5 to 1. The factors of age, sex, color and marital status failed to account for the excess prevalence of syphilis in these two groups.

Recent information concerning biologic false positive serologic reactions suggests, however, that the supposed association of syphilis with cancer of the tongue or cervix may be more apparent than real, perhaps due to the fusospirochetosis often associated with cancer in these areas.

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209. Flax, L.; Levert, E. L., and Strong, R. A.: A Study of Premature Mortality, J. Pediat. **21**:717 (Dec.) 1942.

210. Beerman, H.; Wammock, V. S., and Magnusen, K. B.: Third Generation Syphilis: Review of the Recent Literature and Report of a Probable Case, Am. J. Syph., Gonor. & Ven. Dis. **26**:504 (July) 1942.

211. Levin, M. L.; Kress, L. C., and Goldstein, H.: Syphilis and Cancer: Reported Syphilis Prevalence Among 7,761 Cancer Patients, New York State J. Med. **42**:1737 (Sept 15) 1942.

Syphilis and Lymphogranuloma Venereum.—Mixed infections with syphilis and lymphogranuloma venereum have been studied in detail by May, whose most recent publication [212] throws new light on the association of these two diseases. May believes that when syphilis is accompanied by lymphogranuloma venerum certain characteristic changes in the early lesions of the former disease become manifest. These changes include: clinically detectable lymphangitis, earlier and more extensive local edema and regional lymphadenopathy, changes in the color and shape of the primary chancre, increased local pain and, in general, a more extensive local disease. There is some evidence that the secondary lesions of syphilis may be more diffuse and malignant, and possibly more resistant to treatment. As yet there is no reason to believe that the mixed infection results in more frequent or more precocious involvement of the central nervous system or of the cardiovascular apparatus.

Grace, Shaffer and Rake [213] have found that serums from patients with congenital syphilis who have negative Frei reactions do not fix complement in the presence of antigen from lymphogranuloma venereum virus. Since this contrasts with the frequent occurrence of positive reactions obtained with serums from patients with venereally acquired syphilis, the authors are further confirmed in their belief that during exposure to venereal infection resulting in syphilis a concomitant and often latent infection with lymphogranuloma venereum frequently occurs.

Penile Amebiasis.—Of interest in the differential diagnosis of genital lesions in general and of primary syphilis in particular is the report by Hermann and Berman [214] of a penile ulcer supposedly due to Endamoeba histolytica. Their patient was known to have had amebic dysentery, and amebas were found in the stool. The exudate from the penile ulceration also contained encysted forms of E. histolytica, and the lesion healed after the local use of carbarsone. Serologic reactions for syphilis became positive as the lesion developed, but no therapeutic response to antisyphilitic treatment had been noted, and repeated dark field examinations of the ulcer gave negative results. It seems somewhat incongruous that the encysted form of the parasite are reported, as one might expect trophozoites if the active ulceration were due to amebiasis. The possibility of a biologic false positive reaction for syphilis apparently was not considered.

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212. May, J.: Nueva contribucion al conocimianto de la asociacion sifilo-poradenico, Rev. argent. de dermatosif. **26**:513, 1942.

213. Grace, A. W.; Shaffer, M. F., and Rake, G.: Further Evidence Concerning the Specificity of the Lymphogranuloma Venereum Complement-Fixation Test in Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **27**:44 (Jan.) 1943.

214. Hermann, H. B., and Berman, L. S.: Penile Ulcer Caused by Endameba Histolytica, J. A. M. A. **120**:827 (Nov. 14) 1942.

Book Reviews

Diagnosis of Uterine Cancer by the Vaginal Smear. By George N. Papanicolaou, M.D., and Herbert F. Traut, M.D. Price $5.00. Pp. 47, with 11 color plates. New York: Commonwealth Fund, 1943.

The purpose of this book is directed toward the establishment of an early diagnosis of uterine cancer. Every one appreciates the fact that further improvement in the methods of treatment of uterine cancer is dependent on the establishment of an earlier diagnosis.

The procedure recommended is of value, as demonstrated by the descriptions and records. It is to be used, as the authors state, as an accessory procedure in conjunction with biopsy, curettage and other methods. If it is employed in this manner, it is apparent that a diagnosis can be made earlier than has been customary.

The principal difficulty with the vaginal smear procedure is that there are relatively few workers who have had sufficient experience to interpret accurately the findings. The authors were reticent in making final interpretation of their observations until they had acquired a vast experience. In a real effort to transmit their experience to others, they have used the only practical method, namely, presentation of many excellent colored drawings and photomicrographs.

The detailed descriptions, the straightforward presentation of the findings and interpretations and the great number of good drawings and photomicrographs make this book of great value to both research workers and clinicians who are interested in vaginal smear studies and the early diagnosis of uterine cancer.

Reaction to Injury. By Wiley D. Forbus. Price, $9.00. Pp. 797, with 532 figures. Baltimore: Williams & Wilkins Company, 1943.

It is no mean task to produce an entirely new textbook of pathology, and the author is to be congratulated on his achievement. The present handsome volume, well printed and profusely illustrated with excellent reproductions of gross and microscopic lesions, constitutes according to the publisher's notice only one half of Dr. Forbus' task. Another section is to appear later; this first instalment deals "with the nature and causation of disease and with the resistive reaction: the inflammatory process and all the diseases that arise therefrom." Matters such as tumors will doubtless be dealt with in the subsequent volume. The author approaches his subject from a dynamic standpoint (witness the title), but in the end one looks for good discussions of morphology and histology, and these are very well done. Space might well have been saved by shortening or omitting most of the clinical discussions, which are a duplication of what is found in any textbook of medicine.

Addendum to the Chemistry of the Amino Acids and Proteins. Edited by Carl L. A. Schmidt. Price, $5.00. Pp. 255. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

Instead of a revision of the "Chemistry of the Amino Acids and Proteins," this addendum was published. It brings up to date some of the salient advances made in the field of protein chemistry since 1937, when the original book was written.

Practically every chapter has been revised and corrections made on the original text. At the end of each chapter there is a complete bibliography of the publications from which the data were drawn. The authors have adhered to their previous level of clear presentation of their respective problems. The addendum is certainly to be recommended to all who are interested in the advances in protein chemistry for the past four years. It is really a small book in itself, written by investigators active in the field. The authors should be encouraged to keep the book up to date, perhaps preferably by making a complete revision of the original book in the future, if possible.

Clinical Parasitology. By Charles Franklin Craig and Ernest Carrol Faust. Third Edition. Price, $9. Pp. 750, with 284 engravings and 4 colored plates. Philadelphia: Lea and Febiger, 1943.

This handsomely gotten up book of 750 pages is too long to review in detail. However, the names of Craig and Faust would seem to promise a happy combination of expert knowledge on the subject of clinical parasitology. The book is comprehensive, well written and excellently illustrated. There is a thorough bibliography. The section on arthropods and human disease seems specially valuable, as this part of the subject is slighted in many textbooks.

An Introduction to Medical Mycology. By George M. Lewis and Mary E. Hopper. Second Edition. Price, $6.50. Pp. 342. Chicago: The Year Book Publishers, Inc.

It is pertinent that a simplified, yet complete, manual on human mycology be available at this time, as there is a marked increase in the incidence of mycotic disease among the members of the armed forces. Dermatophytosis and other mycotic diseases among these men often produce considerable disability and loss of valuable time.

The first edition of this book was printed four years ago and has become well accepted as a guide to elementary human mycology. The second edition has been enlarged and rewritten in part. There are many added colored and halftone illustrations. The chapters on the passive transfer test and the data on the trichophytin, oidiomycin, coccidioidin, blastomycin and sporothricin tests, as well as the information on histoplasmosis, have been brought up to date. The authors have simplified the classification of fungous diseases so that the way is cleared for ready diagnosis by those who have only a practical interest in human mycology. They have gathered and simplified the available practical methods of diagnosis and therapeutics on human mycology and have evaluated these procedures in the light of their own extensive experience.

The book is divided into two parts. The first deals with the clinical, theoretic and experimental aspects of mycology, and the second deals with laboratory methods useful for the diagnosis of fungous diseases. The latter section presents detailed and precise methods for identifying fungi. The exact formulas for the simpler types of culture mediums are given. Directions for the construction, purchase and diagnostic use of filtered ultraviolet rays are presented. All procedures advised are simple and practical for office use. At the end of each chapter there is a short bibliography which is sufficiently inclusive to give ready access to the available literature on those subjects discussed. None of the discussions are long or involved or inclusive enough to permit a detailed or complete consideration of any one subject. For complete information the reader must resort to the bibliography. The book is to be recommended as a good elementary manual of practical human mycology.

Rehabilitation of the War Injured. Edited by William Brown Doherty and Dagobert D. Runes. Price, $10. Pp. 684, with 240 figures. New York: The Philosophical Library, 1943.

This symposium includes over fifty articles on various aspects of rehabilitation. The main subject headings concern neurology and psychiatry, reconstructive and plastic surgery, orthopedics, physical therapy, occupational therapy and vocational guidance, and legal aspects of rehabilitation. Such names as Denny-Brown, Stanley Cobb, Vilray Blair, Frank Krusen and William Lennox among the authors give an idea of the authoritative character of the work, although most of the articles are fairly brief and general. The volume is well printed but rather poorly illustrated. An index would be useful.

The Common Form of Niacin Amide Deficiency Disease: Aniacinamidosis. By William Kaufman. Price, not given. Pp. 62. Bridgeport, Conn.: Yale University Press, 1943.

This little volume, privately printed, expresses the views of the author on nicotinc acid deficiency, a condition which he refers to as "aniacinamidosis." An elaborate syndrome is described. The author himself states that "lacking adequate laboratory facilities I can submit no rigorous clinical or laboratory proof" that the conditions described are entirely due to niacin deficiency.